

Effect of serotonin-norepinephrine reuptake inhibitors for patients with chemotherapy-induced painful peripheral neuropathy

A meta-analysis

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Abstract

Background: To compare the efficacy of serotonin-norepinephrine reuptake inhibitors (SNRIs) treatment for chemotherapy-induced peripheral neuropathy (CIPN)

Methods: Two authors independently searched MEDLINE, Embase, Cochran Library, and Web of Science to identify and review articles published from January 1998 until December 2018 according to selection criteria. Outcomes were expressed as mean difference, the pooled odds ratio, or relative risk in a meta-analysis model.

Results: A total of 10 studies were included in this meta-analysis: 6 randomized-controlled studies and 4 observational studies. Meta-analysis showed that CIPN was improved after treatment with SNRI (standardized mean difference=2.20; 95% confidence interval, 0.90–3.49; $I^2=93%$ in 3 randomized controlled studies). Somnolence and insomnia occurred in <15% of patients. Incidence of somnolence was lower than with pregabalin treatment, and insomnia was comparable to that in expectant management or pregabalin treatment. Incidence of nausea and vomiting was higher than in expectant management, but no significant difference was found when compared to expectant management.

Conclusion: From the several available studies suitable for indirect comparison, SNRI shows excellent efficacy and tolerability to CIPN. SNRI could provide an important treatment option for CIPN.

Abbreviations: CI = confidence interval, CIPN = chemotherapy-induced peripheral neuropathy, ORs = odds ratios, RCTs = randomized clinical trials, RRs = risk ratios, SMD = standardized mean difference, SNRIs = serotonin-norepinephrine reuptake inhibitors.

Keywords: serotonin-norepinephrine reuptake inhibitors, chemotherapy, peripheral neuropathy

1. Introduction

Peripheral neuropathy is a debilitating and painful condition that occurs with destruction and dysfunction of the motor, sensory, and autonomic peripheral nerves.^[1] Certain chemotherapy

classes (platinum agents, taxanes, vinca alkaloids, epothilones, immunomodulators, and proteasome inhibitors) are known neurotoxins.^[2] These agents cause damage to peripheral nerves by destroying microtubules and interfering with microtubule-based

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axonal transport, which results in chemotherapy-induced peripheral neuropathy (CIPN).^[2,3] Upward of 40% of patients receiving these chemotherapies may develop CIPN.^[2] Although some patients with CIPN have complete symptom resolution over time or with discontinuation of treatment, most patients have long-term morbidity and decreased quality of life.^[3]

It is known that neurotransmitters such as serotonin and norepinephrine are involved in the descending inhibitory nociceptive pathway and can amplify the effects of central sensitization.^[3] Because serotonin-norepinephrine reuptake inhibitors (SNRIs) inhibit the reuptake of these neurotransmitters, synaptic concentrations increase, and prevent input to the spinal dorsal horn neurons, which results in decreased pain transmission.^[3] Previous studies showed that SNRIs, specifically, venlafaxine and duloxetine, are effective treatments for painful diabetic neuropathy.^[4–6] Based on these trials, some studies were conducted to show that SNRI would ameliorate CIPN pain as well.^[7–9] Therefore, the objective of our study was to provide a comprehensive evaluation of the efficacy and adverse events of SNRI treatment for CIPN.

2. Materials and methods

This study is based on the Cochrane Review Methods, and reporting follows the Meta-analysis of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.^[10] The protocol of this study was registered on the PROSPERO website in February 2019 (registration number CRD42019119812). This was a retrospective study in which only data that were publicly available were included without any personal information of individual patients. Thus, the institutional review board concluded that the approval was not applicable for this study.

2.1. Data sources

In September of 2018, we did a comprehensive literature search. We conducted electronic searches in the MEDLINE, Embase, Cochran Library, and Web of Science. We also conducted searches in a regional electronic bibliographic database (KoreaMed). No restrictions were imposed in terms of the publication language, time, or status. The search strategy was designed for searching MEDLINE through the PubMed interface. The following keywords were used: “chemotherapy,” “peripheral neuropathy,” and “serotonin-norepinephrine reuptake inhibitors.” Electronic database searches used both free-text words and Medical Subject Headings. The search strategy was adapted as appropriate for all other databases searched, taking into account differences in indexing terms and search syntax for each database. The comprehensive search strategies are described in the supplemental file (Supplementary 1, <http://links.lww.com/MD/D560>). We identified further relevant studies for possible inclusion in our review by reviewing the reference lists of the studies identified by our initial search strategies.

We used the following study-inclusion criteria: studies with patients taking SNRI for CIPN; prospective case–control studies that compared SNRI to control for CIPN; and parallel-design studies in which researchers compared outcomes of CIPN with and without SNRI treatment. The exclusion criteria were studies in which the researchers included women who were not diagnosed with CIPN, or which did not use SNRI, did not evaluate CIPN, or did not report the effect of SNRI.

2.2. Data extraction

The 2 reviewers independently did data extraction using a predefined data extraction form. Any disagreement unresolved by discussion was reviewed by a 3rd author. The following variables were extracted from the studies:

1. demographic characteristics such as the number and sex of the patients,
2. age at the time of treatment,
3. types of cancer,
4. follow-up period after treatment,
5. intervention protocol,
6. types of treatment drugs, and
7. measurements of treatment outcomes (Table 1).

The outcomes of SNRIs treatment for CIPN that were used in the meta-analysis were as follows: percentage of patients who experienced reduction of pain after treatment; the change of neuropathic pain score by a scoring system that quantifies the degree of pain; and percentage of patients who complained of somnolence, insomnia, or nausea and vomiting after treatment.

Of the 10 studies, 6 were prospective randomized clinical trials (RCTs) and 4 were retrospective observational studies. All 6 RCTs reported the results based on the scoring system before and after treatment, whereas Durand et al and Zimmerman et al did not show standard deviations or errors, and therefore they were not included in the quantitative analysis.^[7,11]

2.3. Assessment of methodologic quality

2.3.1. Assessment of risk of bias. We assessed quality with different tools appropriate for the design of each study. RCTs were assessed with the Cochrane risk of bias assessment tool, and observational studies were assessed with the Newcastle-Ottawa scale.^[12] The Cochrane risk of bias assessment tool grades each type of risk as low, high, or unclear. Types of risk include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential source of bias. We considered studies without a high risk of bias in any category to be of good quality, and considered studies with 1 high risk or 2 unclear risks to be of fair quality. The rest were considered to be of poor quality.

The Newcastle-Ottawa scale has three domains: selection, comparability, and outcome. In the selection domain, 1 star can be given to each category: representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study. In comparability, a maximum of 2 stars can be given according to the comparability of cohorts on the basis of the analysis. In outcome, 1 star can be given to each category: outcome assessment, adequacy of the length of follow-up, and the follow-up of cohorts. Studies with more than three stars in the selection domain, 1 or 2 stars in the comparability domain, and more than 2 stars in the exposure/outcome domain were considered to be of good quality.

2.4. Statistical analysis

We carried out statistical analysis with RevMan software (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We calculated dichotomous outcomes with risk ratios (RRs) or odds ratios (ORs) with a 95% confidence interval (CI). We calculated continuous outcomes

Table 1

Characteristics of the included studies.

Study	Study design	Type of cancer	Participants (n)	Age	Sex (female)	Follow-up period	Type of drug	Outcome
Durand, 2012	Randomized, double-blind, placebo-controlled phase III trial	Any type of cancer	24	67.9 (32-82.7) Median (range)	37.5%	NA	Venlafaxine 50 mg (pretreatment) → ChemoTx → venlafaxine 37.5 mg bid (days 2-11)	Venlafaxine has clinical activity against oxaliplatin-induced acute neurosensory toxicity (NPSI, NRS)
Yang, 2012	Open-label, single-arm pilot study	Stages III-IV colorectal cancer	39	64.8 (34-83) Mean (range)	43.6%	12 wk	Duloxetine 30 mg → 60 mg 12 wk	Feasible in treatment of OIPN with tolerable toxicity at daily dose of 60 mg/d (VAS, NCI-CTCAE)
Smith, 2013	Randomized, double blind study	Any type of cancer	109	60 ± 10.4	65%	5 wk	Duloxetine	Use of duloxetine compared with placebo resulted in a greater reduction in pain
Hirayama, 2015	Open-label, randomized, crossover	Any type of cancer	34	61 (48-75) and 64 (49-75) Median (range)	52.9%	4 wk	Duloxetine 20 mg 1 wk → 40 mg 3 wk or vitamin D	Duloxetine has a beneficial effect on CIPN caused by oxaliplatin, pectitaxel, vincristine, or bortezomib (VAS)
Otake, 2015	Retrospective	Gynecological cancer	25	62 (40-77) Median (range)	100%	NA	Duloxetine	Duloxetine can be effectively used for pectitaxel induced peripheral neuropathy in patients with gynecologic cancers
Kus, 2016	Retrospective	Any type of cancer	91	52.88 mean	79.76%	9 wk	Venlafaxine	Significant clinical activity against taxane-oxaliplatin-induced acute neurosensory toxicity
Zimmerman, 2016	Randomized, placebo-controlled	Colon cancer	50	62.3 mean	46%	12 mo	Venlafaxine	Neither supports the use of venlafaxine for OIPN in clinical practice nor the initiation of a phase III trial to investigate venlafaxine in this setting
Kanbayashi, 2017	Retrospective	Any type of cancer	74	61 (29-68), n = 7 63 (23-81), n = 21 58 (22-77), n = 46 NA	33.8%	2 wk	Duloxetine	Duloxetine was effective in 28 of 74 patients
Avan, 2018	Randomized, double-blind trial	Breast cancer	82	NA	100%	6 wk	Pregabalin and duloxetine	Pregabalin as well as duloxetine improve the global QOL of breast cancer patients with TIPN
Farshtain, 2018	Open-label randomized trial	Any type of cancer	52 (duloxetine), 52 (venlafaxine)	57.44 (± 14.53) venlafaxine, 63.85 (± 7.58) duloxetine	71% (duloxetine), 86.5% (venlafaxine)	4 wk	Duloxetine (30 mg), venlafaxine (37.5 mg) 1 mo	Duloxetine seems to be more effective than venlafaxine in decreasing the symptoms of chemotherapy-induced peripheral neuropathy. Duloxetine was more effective than venlafaxine in decreasing motor neuropathy and neuropathic pain grade

ChemoTx = chemotherapy, CIPN = chemotherapy-induced peripheral neuropathy, mo = months, NA = not applicable, NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events, NPSI = Neuropathic Pain Symptom Inventory, NRS = numeric rating scale, OIPN = oxaliplatin-induced peripheral neuropathy, QOL = quality of life, TIPN = Taxane-induced peripheral neuropathy, VAS = visual analog scale, wk = weeks.

with mean difference or standardized mean difference (SMD) with 95% CIs. We used an inverse variance weighting approach to evaluate the difference before and after SNRI treatment. When data were reported with median and range or interquartile range, we calculated the mean and standard deviation.^[13] Heterogeneity was calculated with I^2 statistics in which an I^2 value exceeding 50% was considered to reveal substantial heterogeneity. We used a random-effect model when there was substantial heterogeneity, but otherwise used a fixed-effect model. We did subgroup analysis according to the study designs and other heterogeneity due to differences in study protocol. We did not use a Funnel plot or other tools such as Egger test for assessing publication bias, because there were few included studies: 6 RCTs^[7,9,11,14–16] and 4 retrospective cohort studies.^[17–20] We carefully discussed the possible effect of publication bias on the outcomes.

3. Results

3.1. Identification of studies

The database searches produced 935 articles (Fig. 1), and 134 duplicated articles were excluded. Of the remaining 801 articles, we excluded 760 publications because it was clear from the title and abstract that they did not meet the inclusion criteria. We obtained full manuscripts for the remaining 39 articles, and after scrutiny of these, we identified 10 potentially relevant studies: 6 RCTs^[7,9,11,14–16] and 4 observational studies.^[17–20]

Characteristics of the included studies are listed in Table 1. A total of 632 patients who were treated with SNRI for CIPN

were included, with 229 patients from the 4 observational studies. The authors of the included studies used different methods to report the women's ages (i.e., mean with SD for each group; mean with SD for all included women; median with range for each group; median with range for all included women; range for each group). In most of the studies, mean or median age of the patients was 60 to 65 years. Types of cancer were heterogenous among the studies: any type of cancers in 6 studies, colorectal cancer in 2 studies, breast cancer in 1 study, and gynecologic malignancies in 1 study. Types of chemotherapy agents were also heterogenous among the studies depending on the type of cancer. Two types of SNRI were used to treat CIPN: duloxetine in 6 studies and venlafaxine in 3 studies. One study compared the effects of venlafaxine and duloxetine on CIPN. Quality assessment of all studies is described in Tables 2 and 3. Among the 6 RCTs, 4 were of good quality and 2 were of poor quality (Table 2). All of the 4 observational studies were of fair quality (Table 3).

3.2. Meta-analysis of the outcomes of SNRI for CIPN

3.2.1. Primary outcome: efficacy of SNRI. Eight trials^[9,14–20] involving 558 patients (329 patients in RCTs and 229 patients in observational studies) measured the efficacy of SNRI in terms of reducing neuropathic pain. Among those, 4 observational studies and 1 RCT reported the number of patients who experienced reduction of neuropathic pain after SNRI treatment. The percentage of patients with pain reduction were 63.6%,^[17] 56%,^[18] 51.9%,^[19] 45.2%,^[20] and 58.8%.^[9] Three RCTs

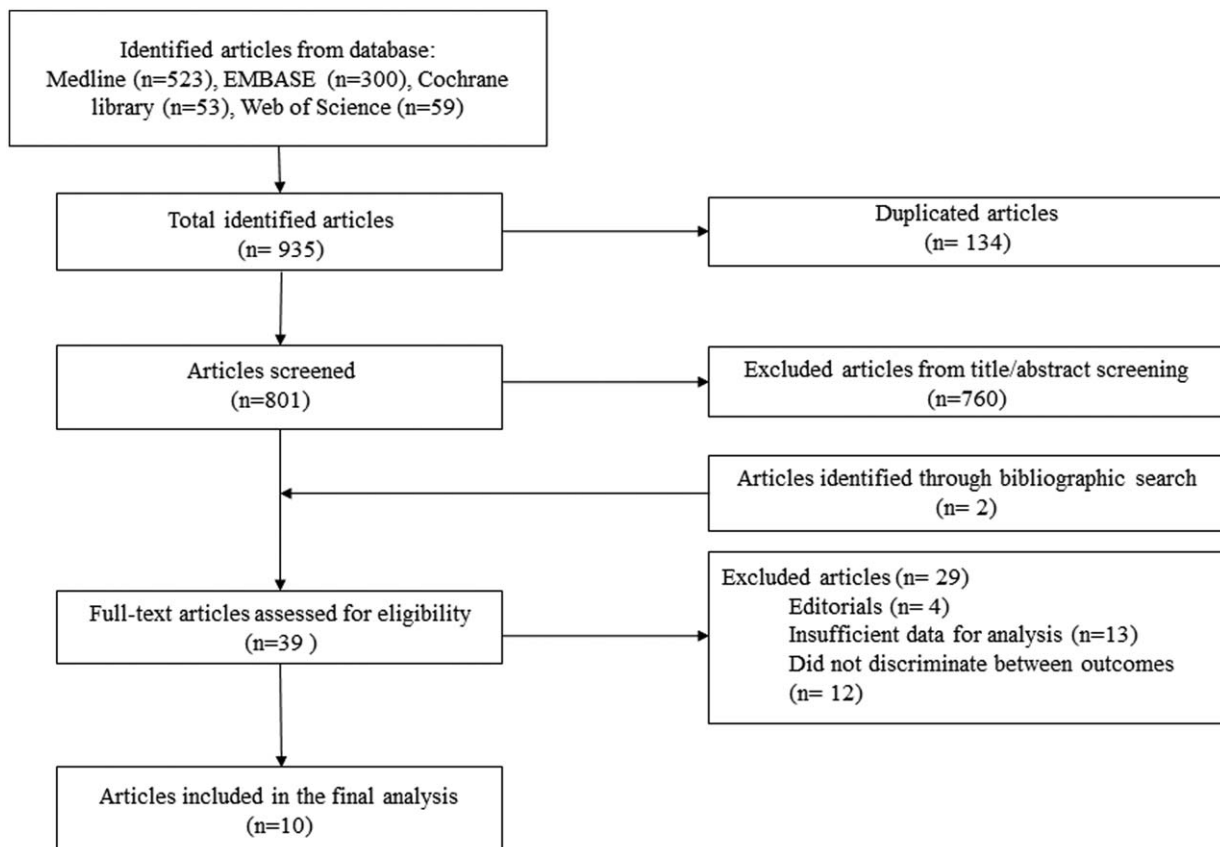


Figure 1. Flow chart outlining the selection of patients.

Table 2
Risk of bias of included randomized controlled study using the Cochrane risk of bias assessment tool.

	Avan 2018	Durand 2012	Farshchian 2018	Hirayama 2015	Smith 2013	Zimmerman 2016
Random sequence generation (selection bias)	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
Allocation concealment (selection bias)	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
Blinding of participants and personnel (performance bias)	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Blinding of outcome assessment (detection bias)	Low risk	Unclear risk	Unclear risk	High risk	Unclear risk	Unclear risk
Incomplete outcome data (attrition bias)	Low risk	Low risk	High risk	High risk	Low risk	Unclear risk
Selective reporting (reporting bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Other bias	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk

Table 3
Quality assessment of included cohort studies using the Newcastle-Ottawa scale.

	Kanbayashi 2017	Kus 2016	Otake 2015	Yang 2012
Selection				
Representativeness of exposed cohort	*	*	*	*
Selection of nonexposed cohort	*	*	*	*
Ascertainment of exposure	*	*	*	*
Outcome not present at the start of the study	*	*	*	*
Comparability	**		**	
Outcome				
Assessment of outcomes	*	*	*	*
Length of follow-up	*	*	*	*
Adequacy of follow-up	*	*	*	*
Total	*****	*****	*****	*****

showed a difference in pain scores between before and after SNRI treatment. Avan et al used EORTC-QLQ-C30, which scores pain in a range from 0 (no pain) to 100 (worst pain).^[15] Hirayama et al used visual analog scale, which scores pain from 0 (no pain) to 10 (worst pain).^[16] Smith et al used the Brief Pain Inventory-Short Form, which also has similar 0 to 10 scoring.^[14] As shown in Figure 2, CIPN was significantly improved after treatment with SNRI (SMD = 2.20; 95% CI, 0.90–3.49; $I^2 = 93\%$).

3.2.2. SNRI vs expectant management. Three RCTs compared SNRI and expectant management for CIPN in terms of pain relief.^[9,14,16] Among those, Smith et al used the Brief Pain Inventory-Short Form and Hirayama et al used visual analog scale to evaluate neuropathic pain, as mentioned previously. Farshchian et al evaluated the number of patients with different grades of neuropathic pain assessed by the Radiation Therapy Oncology Group classification, which grades neuropathic pain from 0 (no pain) to 4 (most severe pain). The analysis of these studies is shown in Figure 3. CIPN was significantly decreased

with SNRI more than by expectant management (SMD = -2.16; 95% CI, -3.26 to -1.06; $I^2 = 84\%$)

3.2.3. SNRI vs pregabalin. One RCT compared SNRI and pregabalin.^[15] According to Avan et al, pregabalin was significantly more effective in reducing pain assessed with EORTC-QLQ-C30 (MD = 13.78; 95% CI, 11.64–15.92, Fig. 4).

3.2.4. Duloxetine vs venlafaxine. One RCT compared duloxetine and venlafaxine.^[9] Administration of venlafaxine was more effective than duloxetine in reducing neuropathic pain (RR = 0.80; 95% CI, 0.70–0.92, Fig. 5).

3.3. Secondary outcome: adverse events

3.3.1. Somnolence. The studies comparing somnolence after SNRI treatment were 2 RCTs^[15,16] and 3 observational studies (Table 4).^[17,18,20] Except for one study by Otake et al, in which 12% of patients complained of somnolence,^[18] the percentage of patients who complained of somnolence was <10% (6.66%,^[17] 5.88%,^[16] 4.76%,^[15] and 3.57%^[20]) As shown in Figure 6, 1

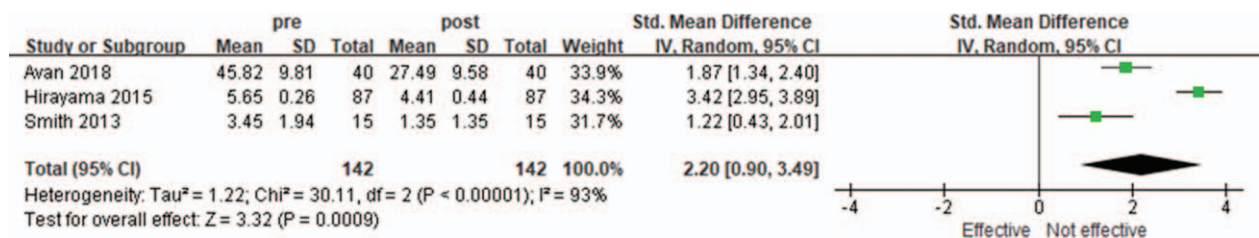


Figure 2. Changes in subjective assessment score of neuropathic pain after serotoninnorepinephrine reuptake inhibitors. CI = confidence interval, SD = standard deviation.

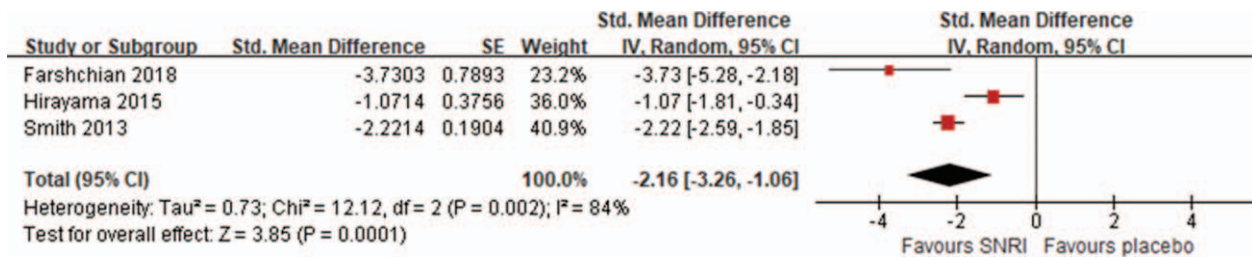


Figure 3. Compare serotonin-norepinephrine reuptake inhibitor (SNRI) and expectant management for chemotherapy-induced peripheral neuropathy in terms of pain relief. CI = confidence interval, SD = standard error.

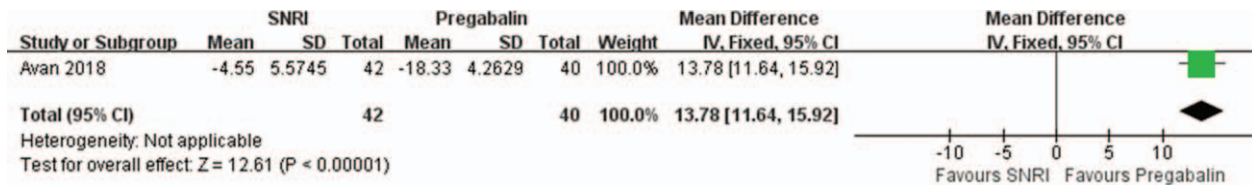


Figure 4. Compare serotonin-norepinephrine reuptake inhibitor (SNRI) and pregabalin treatment for chemotherapy-induced peripheral neuropathy in terms of pain relief. CI = confidence interval, SD = standard deviation.



Figure 5. Compare duloxetine and venlafaxine treatment for chemotherapy-induced peripheral neuropathy in terms of pain relief. SNRI: serotonin-norepinephrine reuptake inhibitors. CI = confidence interval.

RCT compared incidence of somnolence between SNRI and pregabalin treatment.^[15] The rate of somnolence was significantly decreased in patients treated with SNRI compared to pregabalin (RR = 0.21; 95% CI, 0.05–0.92).

3.3.2. Insomnia. Insomnia was reported in 3 RCTs^[14–16] and 3 observational studies.^[7,17,20] One RCT^[16] and 1 prospective observational study^[17] reported that 5.88% and 6.67% of patients complained of insomnia, respectively. Other than these 2 studies, insomnia occurred in <5% of patients.^[14,15,20] In 1 RCT, none of the patients complained of insomnia after SNRI treatment.^[7] There was no significant difference of the rate of insomnia between SNRI and expectant treatment in 2 RCTs (RR = 0.59; 95% CI, 0.21–1.63, Fig. 7A).^[7,14] There was also no significant difference of the rate of insomnia between SNRI and

pregabalin treatment in 1 RCT (RR = 4.77; 95% CI, 0.24–96.34, Fig. 7B).^[15]

3.3.3. Nausea and vomiting. Nausea and vomiting were reported in four RCTs^[7,14–16] and 3 observational studies.^[17,18,20] The incidence of nausea and vomiting differed between studies. In 1 RCT, only 0.46% of patients reported nausea and vomiting,^[14] but Durand et al reported that 91.66% of patients had nausea and vomiting.^[7] Also, Durand et al reported nausea and vomiting were significantly increased after SNRI treatment more than by expectant management (RR = 1.57; 95% CI, 1.10–2.25, Fig. 8A).^[7] There was also no significant difference of the rate of nausea and vomiting between SNRI and pregabalin treatment in 1 prospective study (RR = 8.58; 95% CI, 0.48–154.45, Fig. 8B).^[15]

Table 4
Percentage of patients with various types of side effects after serotonin-norepinephrine reuptake inhibitors treatment.

	Avan 2018	Durand 2012	Hirayama 2015	Kus 2016	Otake 2015	Smith 2013	Yang 2012
Somnolence	4.76% (2/42)	NA	5.88% (2/34)	3.57% (3/84)	12% (3/25)	NA	6.66% (2/30)
Insomnia	4.76% (2/42)	0%	5.88% (2/34)	1.19% (1/84)	NA	4.59% (5/109)	6.67% (2/30)
Nausea/vomiting	9.52% (4/42)	91.55% (22/24)	8.82% (3/34)	3.57% (3/84)	4% (1/25)	0.46% (5/109)	13.33% (4/30)

*Data are presented as % (number of patients with side effect/total number of patients who were treated with serotonin-norepinephrine reuptake inhibitors).



Figure 6. Compare adverse reaction after serotonin-norepinephrine reuptake inhibitor (SNRI) treatment in terms of somnolence. CI = confidence interval.

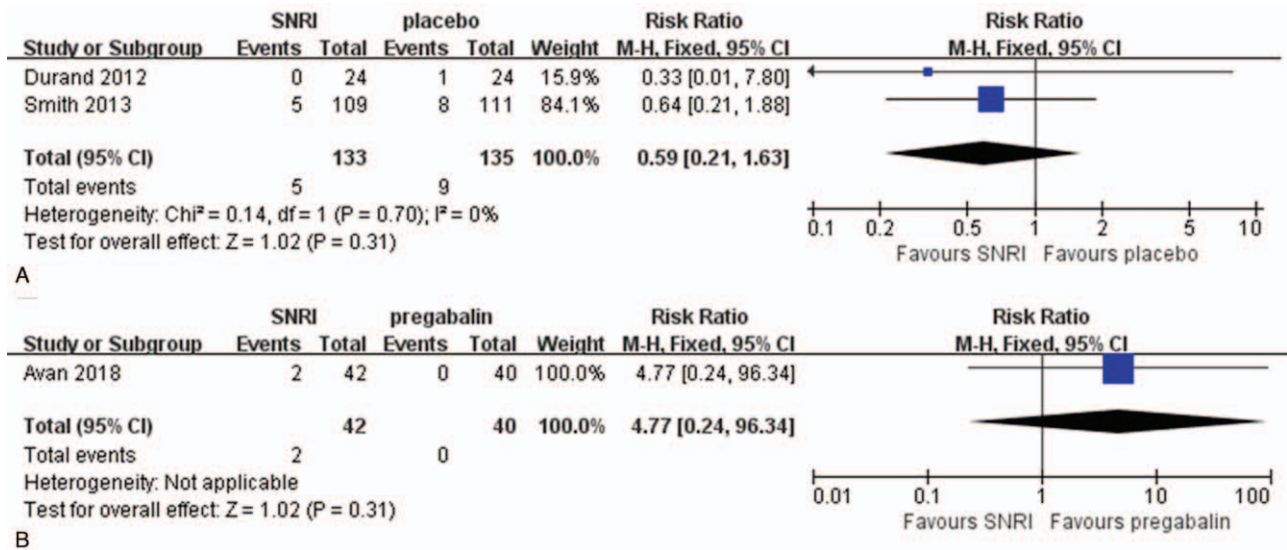


Figure 7. Adverse reaction in terms of insomnia (A) compare serotonin-norepinephrine reuptake inhibitor (SNRI) treatment and expectant management (B) compare SNRI and pregabalin.

3.3.4. Other adverse events. Other adverse events such as dizziness, headache, fatigue, dysgeusia, and constipation after SNRI treatment have been reported. Avan et al reported higher incidence of dizziness after duloxetine treatment

compared to pregabalin treatment (17.5% vs 0%, respectively).^[15] However, Kus et al reported only 2.4% of patients experienced dizziness after duloxetine treatment.^[20] Similarly, Durand et al reported 2% of patients complained dizziness

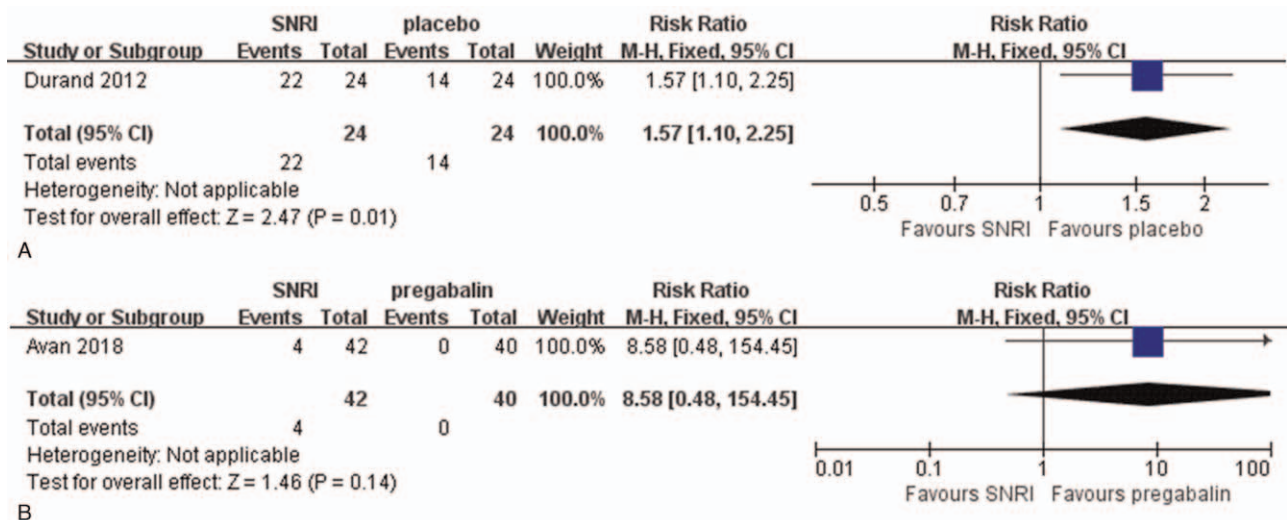


Figure 8. Adverse reaction in terms of nausea and vomiting (A) compare serotonin-norepinephrine reuptake inhibitor (SNRI) treatment and expectant management (B) compare SNRI and pregabalin.

after venlafaxine treatment, which was even lower than placebo group (4.9%).^[17] Headache after venlafaxine treatment was only reported by Durand et al, and the incidence was comparable to the placebo group (2% in venlafaxine group vs 1.6% in placebo group).^[17] Incidence of dysgeusia and constipation was reported to be 4% after duloxetine treatment in the study by Otake et al.^[18] However, Durand et al reported no incidence of dysgeusia or constipation after venlafaxine treatment.^[17]

4. Discussion

The development of chemotherapeutic agents has increased the survival period of patients with malignancies. However, a significant increase of CIPN due to toxic chemotherapeutic agents has become a major factor that lowers the quality of life for cancer patients. Treatment of painful CIPN continues to be a challenge, because most drugs tested to date have fallen short of providing adequate pain relief.^[21–24] To treat CIPN, SNRIs that decrease pain transmission via inhibition of serotonin and norepinephrine have been suggested by many studies. Durand et al showed that venlafaxine was effective in reducing CIPN.^[25,26] Matsuoka et al showed duloxetine was effective for cancer patients with CIPN who are not responsive to pregabalin,^[27] and several randomized trials are ongoing to prove the effect of duloxetine for patients with CIPN.^[28,29] Based on these findings, we quantitatively analyzed 6 prospective and four retrospective studies to elucidate the efficacy of SNRI for painful CIPN. In this study, SNRI was significantly effective for the relief of CIPN. The incidence of adverse effects such as somnolence and insomnia after SNRI treatment was <15% and was comparable to that from expectant management or pregabalin treatment. The incidence of nausea and vomiting was diverse in this meta-analysis; 1 RCT reported a high incidence of nausea and vomiting that was significantly increased compared to expectant management.^[15,25] However, the percentages of patients reported by other studies were <15%, and 1 study reported a decreased incidence of nausea and vomiting compared to pregabalin treatment.^[15] Therefore, we recommend SNRI as a rescue therapy for neuropathic pain after neurotoxic chemotherapy.

Only 1 randomized controlled trial compared SNRI to pregabalin.^[15] That study reported that pregabalin was significantly more effective in reducing neuropathic pain.^[15] However, both pregabalin and duloxetine equally improved the global QOL of patients over a 6-week trial in that study.^[15] Although improvement of pain and insomnia domain of QOL was better with pregabalin, duloxetine was superior in improvement on the emotional functioning subscale of QOL. Moreover, other studies reported that the efficacy of duloxetine was 1.27 times that of pregabalin in the improvement of diabetic neuropathic pain.^[30,31] Therefore, further studies are needed to confirm the efficacy of SNRI and pregabalin for CIPN.

Previous studies reported that several adverse events occurred in at least 5% of duloxetine-treated participants; these common adverse events included somnolence, nausea, dizziness, malaise, and vomiting.^[32,33] In this study, adverse effects such as somnolence, and insomnia were not common after SNRI treatment. Except for the study by Otake et al,^[18] the incidence of somnolence was reported to be about 5%.^[15–17,20] Likewise, the incidence of insomnia was reported to be about 5%,^[14–17,20] and none of the patients complained about insomnia after treatment in Durand et al (0%).^[17] The incidence of nausea and

vomiting differed greatly between the included studies. Durand et al reported a high incidence of nausea and vomiting (91.66%), which was significantly more than for expectant management.^[7] However, the percentages of patients reported by other studies were <15%,^[7,14–18,20] with the lowest incidence of 0.46%.^[14] In Avan et al, the incidence of nausea and vomiting was less than from pregabalin treatment.^[15] Although SNRI appears to be feasible compared to expectant management or pregabalin treatment in terms of somnolence and insomnia, more research is needed to see the effect of SNRI on nausea and vomiting.

In this study, only one randomized controlled trial compared duloxetine and venlafaxine and reported that duloxetine was more effective than venlafaxine in decreasing motor neuropathy and neuropathic pain grade, since duloxetine produced better reduction of cranial, motor, sensory neuropathy, and neuropathic pain.^[9] However, 1 limitation of this study was the small sample. This limitation can justify some of the insignificant comparisons. Therefore, we recommend that further studies with larger samples be conducted to confirm these results.

This study has several limitations. First, we included only a few studies, and second, the studies included were heterogeneous not only in study designs, but also in chemotherapy agents, cancer type, and type of SNRIs. Third, there may be some exaggerated effect of SNRI due to publication bias. We acknowledge that some exaggeration of the effect of SNRI on pain reduction might be present. We decided not to use a Funnel plot or other tools such as Egger test for assessing publication bias, because there were few included studies, according to the opinion of statisticians about the statistical analysis. However, this is the 1st meta-analysis to evaluate the efficacy of SNRI in patients with CIPN and did not apply any restrictions according to study types, language, or time, to draw conclusions not skewed to one side.

In conclusion, from the several available studies suitable for indirect comparison, SNRI shows excellent efficacy and tolerability for CIPN. Therefore, SNRI could provide an important treatment option for CIPN.

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