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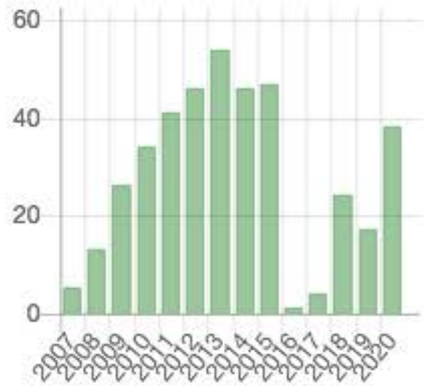

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Abstract

Background: One of the adverse effects of chemotherapy in the neurological field is chemotherapy-induced peripheral neuropathy (CIPN), it was an adverse effect caused by many chemotherapeutic regimens and a major cause of continuous pain in patients who survived cancer. When the symptoms get worse, survivor's quality of life is declining and they are often having problems with mental health, insomnia, cognitive functioning, fatigue, physical functioning, and pain. So far the choice of therapy for CIPN is still limited. Now, there was no drug approved to treat pain due to CIPN. Duloxetine are a SNRI (serotonin norepinephrine reuptake inhibitor), which it's useful in CIPN are highly supported by evidence.

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Methods: We conducted a systemactic-computer based literature search on January 4, 2019 in PubMed database for article published between 2013 and 2018. We searched for a literature related with used a duloxetine for management of chemotherapy induced peripheral neuropathy.

Results: From the 4 studies that included in this review, the total participants are 478 patients with neuropathic pain and already get a chemotherapy regiment. From the meta-analysis showed one study had no effect, two studies had small effect, and one study had medium effect.

Conclusion: Duloxetine is a great option for the treatment of CIPN in especially reducing neuropathic pain.

Keywords

Pain. Neuropathic pain, chemotherapy induced peripheral neuropathy, cancer, duloxetine.

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I Putu Eka Widyadharma[1], Chiquita Putri Vania Rau[1], Rizaldy Taslim Pinzon[2], Yudiyanta[3], Agung Wiwiek Indrayani[4], Thomas Eko Purwata[1], Boya Nugraha[5]

Correspondence: *eka.widyadharma@unud.ac.id*
[1]*Departement of Neurology, Faculty of Medicine, Udayana University and Sanglah General Hospital, Bali, Indonesia*
[2]*Departement of Neurology, Faculty of Medicine, Duta Wacana University, Yogyakarta, Indonesia*
[3]*Department of Neurology, Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University, Yogyakarta, Indonesia*
[4]*Department of Pharmacology, Faculty of Medicine, Udayana University, Bali, Indonesia*
[5]*Department of Rehabilitation Medicine, Hannover Medical School, Germany*

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ABSTRACT

Background: One of the adverse effects of chemotherapy in the neurological field is chemotherapy-induced peripheral neuropathy (CIPN), it was an adverse effect caused by many chemotherapeutic regimens and a major cause of continuous pain in patients who survived cancer. When the symptoms get worse, survivor's quality of life is declining and they are often having problems with mental health, insomnia, cognitive functioning, fatigue, physical functioning, and pain. So far the choice of therapy for CIPN is still limited. Now, there was no drug approved to treat pain due to CIPN. Duloxetine are a SNRI (serotonin norepinephrine reuptake inhibitor), which it's useful in CIPN are highly supported by evidence.
Methods: We conducted a systemactic-computer based literature search on January 4, 2019 in PubMed database for article published between 2013 and 2018. We searched for a literature related with used a duloxetine for management of chemotherapy induced peripheral neuropathy.
Results: From the 4 studies that included in this review, the total participants are 478 patients with neuropathic pain and already get a chemotherapy regiment. From the meta-analysis showed one study had no effect, two studies had small effect, and one study had medium effect.
Conclusion: Duloxetine is a great option for the treatment of CIPN in especially reducing neuropathic pain.

Keywords: Pain. Neuropathic pain, chemotherapy induced peripheral neuropathy, cancer, duloxetine.

Introduction

With an estimated 32 million cancer survivors worldwide, it is increasingly important to understand the potential long-lasting impacts of successful cancer treatments. One of the adverse effects of chemotherapy in the neurological field is chemotherapy-induced peripheral neuropathy (CIPN), it is an adverse effect caused by many chemotherapeutic regimens and a major cause of continuous pain in patients who survived cancer.[1]

CIPN symptoms are the same as neuropathy in general. As described in a study in Indonesia, there are five clinical symptoms that are most dominant such as, electric shock like sensations, hyperalgesia, burning sensation, pinprick sensation, and paresthesia.[2] The high success number of chemotherapy for the management of cancer also leads to an increase in the survival numbers of patients. However, also followed by the increasing numbers of patients who survived the cancer and suffers neuropathic pain. Neuropathic pain is pain that arises due to damage from the path of the pain carrier itself, either in the form of impaired function or pathological changes in a nerve.[3] Prevalence of CIPN varies depending on the type of chemotherapy, but in general is estimated about 68% in the short term and 30% in the long term, these development relate to either a single dose or accumulation dose. Chemotherapy agents that most often cause neurotoxic were taxanes and platins, which cause the CIPN on 30%-50% of patients who received the regimens.[4] Infusion-related neuropathic symptoms also occur, particularly with oxaliplatin and paclitaxel regimens.[5,6]

When the symptoms get worse, survivor's quality of life was declining and they are often having problems with mental health, insomnia, cognitive functioning, fatigue, physical functioning, and pain.[7,8] CIPN also has effects in economic field, which caused CIPN leads to higher costs for healthcare.[9] CIPN also effected on the chemotherapy dose reduction, changing, delays, or even cancelation,

hence the pain caused by cancer treatment is a serious health issues.

Neuropathic pain in HIV (Human Immunodeficiency Virus), Chemotherapy Induced Peripheral Neuropathy and Lumbasacral Radiculopathy are often refractory to drugs and until now there are still no drugs that provide satisfactory results.[10] Symptom management is the only action available for handling CIPN. So far the choice of therapy for CIPN is still limited. Now, there was no drug approved to treat pain due to CIPN. For the management of pain caused by cancer therapy, opioids is still the main choice, but less appropriate for chronic pain due to opioids owned a dependence effects. Meanwhile, a group of drugs that called adjuvant analgesic had been introduced for the treatment of chronic pain. Among these are topical agents, antidepressants (venlafaxine, duloxetine, TCA/tricyclic antidepressants), corticosteroids, N-methyl-D-aspartate antagonists, biphosphonates, cannabinoids, and also combination of antidepressants and anticonvulsants drugs (gabapentinoids, like pregabalin and gabapentin).[11] Recently the use of antidepressants and anticonvulsants for CIPN has been increase because it brings the development of the positive results of the patients with fibromyalgia and diabetic neuropathy.[12]

Duloxetine is a SNRI (serotonin norepinephrine reuptake inhibitor), which very useful in CIPN and highly supported by evidence.[13] Duloxetine acts by inhibiting norepinephrine and serotonin synaptic reuptake, make concentrations at the synapse increase then blocks input signals to the spinal dorsal horn neurons, and at the end make pain transmission decrease. Duloxetine also used and approved to reduce pain in patients with diabetic neuropathy.[14]

Several randomized control trials (RCT) had been done to see the effects of duloxetine CIPN. To our knowledge, there are still no systematic review had been done to summarize about these topic yet. So the author decided to assemble a systematic review to summarize this studies about safety and efficacy of duloxetine for management chemotherapy-induced peripheral neuropathy (CIPN) in particular for reducing the pain.

Methods

We conducted a systematic-computer based literature search on January 4, 2019 in PubMed database for article published between 2013 and 2018. We searched for a literature related with used a duloxetine for management of CIPN. We included the following terms as our strategy: (1) ‘‘neuropathy’’, “peripheral neuropathy”, “neuropathic pain”; (2) ‘‘chemotherapy’’, “CIPN”, “chemotherapy-induced”; (3) ‘‘pain’’, ‘‘painful’’; (4) “management”, “therapy”, “treatment”; (5) “duloxetine”, “SNRI”. Potentially relevant studies were also searched from a reference lists in retrieved articles and from Google Scholar.

Articles included for this review required to meet the following criteria: the study was carried out on humans adults (>18 years), patients had neuropathic pain due to chemotherapy, the article must be a research based study with a minimum level of evidence is level II, references using english, published in the last 5 years, and the outcome results included pain reduction and adverse effects (AE). The exclusion criteria are articles that did not provide new data, such as: review articles, case report, letters to the editor and editorials, and also book chapters.

Data were extracted from the published reports using a standard data collection. Characteristics of the article included: (1) patient demographics (sex, age, type of cancer), (2) study characteristics (type of study, study years, country), (3) intervention (comparator, dose of duloxetine, duration of the intervention), (4) outcomes (primary outcomes/pain reduction, with a standard deviation and adverse effects).

Analyses focused on change of the pain intensity on the patients and incidence also severity of the side effects of treatment. Number of patients who experience the adverse effects was results from asking and observing the patients for specific adverse events, like nausea and vomiting.

To obtain reliable conclusions, the included studies must be screened to find potential limitation and to minimize bias. In this review, we used a tool that provided by the Cochrane Collaboration for a risk of bias assessment. Cochrane Collaboration tool is based on several items such as incomplete outcome data, blinding outcome assessment, allocation concealment, and other bias. Based on the area, each study can be classified as unclear risk, low risk, and high risk.[15]

For the analysis and interpretation of the data of the studies selected, the mean value of the final pain and the effect size of each of the studies were calculated, as measurements of central tendency and dispersion. The standard deviation is the statistical element that takes into account both components, which allows to properly weights each study included in the meta-analysis; therefore, it was considered as inclusion criterion that each study had the mean value and the standard deviation for final pain both in the experimental group and in the placebo group.

Because of the variations of the tools that used in included studies, we used Hedge’s g as a standarized measurement of the effect size. This measurement of the effect size does not depend on the standard deviations but based on the g value in absolute value, like mention below[16]:

- 0 - 0.2 = no effect
- 0.2 – 0.5 = small effect
- 0.5 – 0.8 = medium effect
- > 0.8 = large effect

Results

Overview of The Included Trials

The results of this strategy included identification of 181 articles from PubMed and 19 articles from other sources (eg. google scholar and reference lists), of which 18 were selected for retrieval.[17-35] Therefore, 4 papers that used in this review already meet the inclusion criteria.17-20 All of the include studies published between 2013 and 2018. The selection process showed in Figure 1.

From the 4 studies that included in this review, the total participants are 478 patients with neuropathic pain and already get a chemotherapy regiment.[17-20]

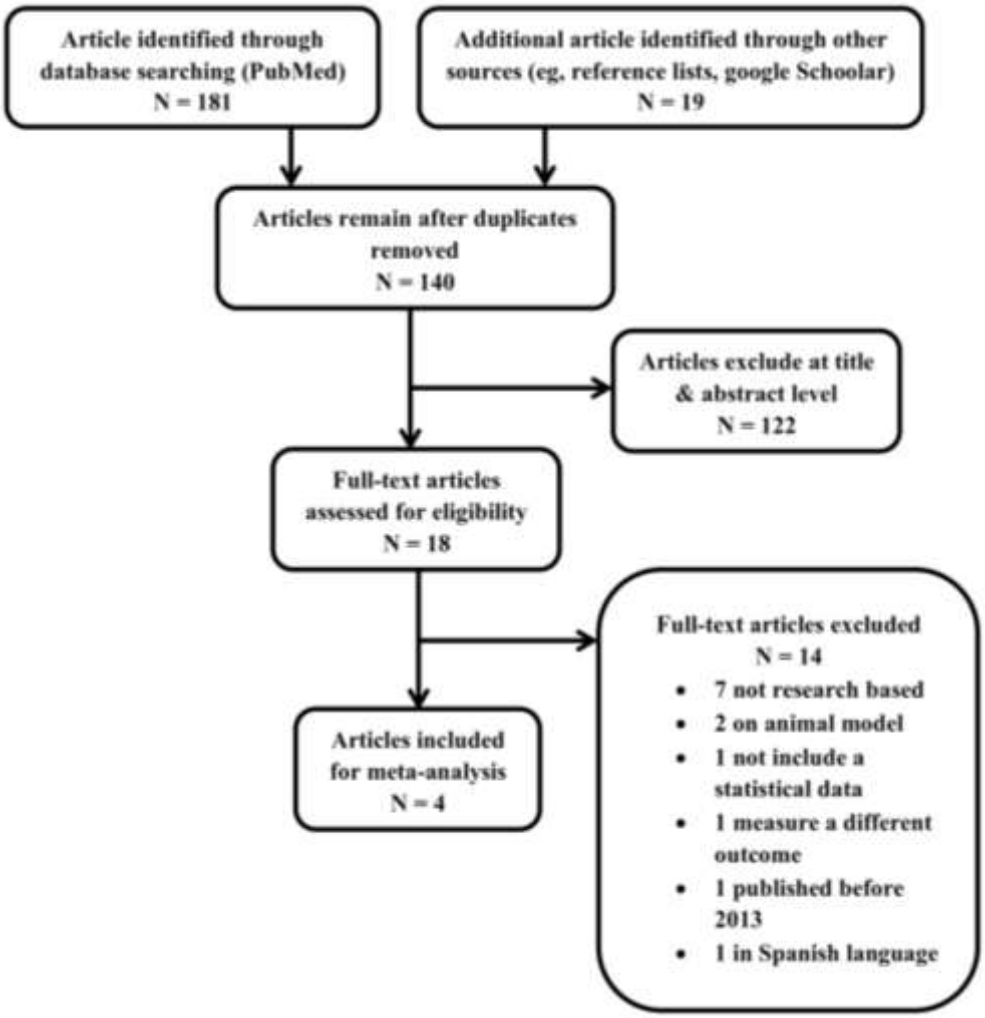

Figure 1. Selection process of the literature from PubMed database and additional sources which then through screening and eligibility process

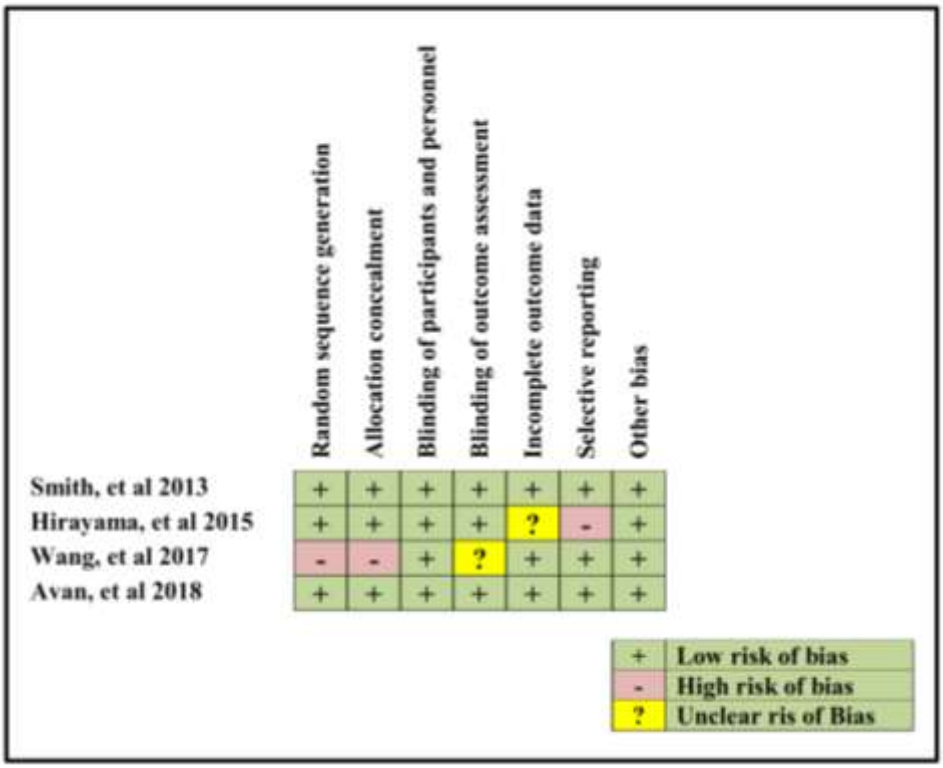

Figure 2. Risk of bias

Table 1 showed the demographic characteristics of these patients. Age of the included patients in this study ranged from 29 to 75 years. Two trials included patients with any type of cancer[17,18] and other two with breast cancer.[19,20]

Accordingly, two trials used various agents17,18; one trials used paclitaxel20; and one trial used paclitaxel or docetaxel19. Study durations varied from 6 to 14 weeks. Dosage of the duloxetine in two studies were orally administered 30 mg daily for 1st week[17,19] meanwhile in the other study 20 mg daily for 1st week18. Continued with 30 mg twice daily19, 40 mg daily18, and 60 mg daily.[17] Only one study that did not mention the duloxetine dose that used in study20. For the comparator, one trial used placebo17, one trial used pregabalin19, one trial compare with Vitamin B1218, and one trial used anti-neurotoxicity drugs20. All the studies[17-20] assessed pain as one of the primary outcome, also included numbness, quality of life, emotional functioning, insomnia, etc. Primary outcome measures that included pain intensity in these study17-20 are: Visual Analog Scale (VAS), FACT-Tax Scales (Functional Assessment of Cancer Therapy-Taxane), BPI (Brief Pain Inventory) pain intensity, and EORTC QLQ-C30 (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire). All the study results that included in this review were then summarized in table 2.

Risk of Bias and Meta-analysis Results

For the risk of bias, according to Cochrane Collaborations, showed in figure 2. Two studies in this review showed "low risk" in all their area and the other two studies have several "high risk" item in the area "Random Sequence Generation", "Allocation concealment", and "Selective Reporting".

Regarding the statistical analysis using Hedge's g, one study showed no effect, which was Avan, et al comparing duloxetine and pregabalin [g: -0.170, 95% CI (-0.604; 0.264)]. Two others studies showed a small effect which are Wang, et al [g: 0.204, 95% CI (-0.184; 0.595)] and Smith, et al [g: 0.422, 95% CI (0.156; 0.690)]. The study by Hirayama et al showed medium effect [g: 0.603, 95% CI (-0.076; 1.302)].

Primary Outcomes

The used of duloxetine for CIPN treatment has been done by Smith et al.,[17] to 231 cancer patients with certain criteria, but only 141 patients who finish this trial. This study claims as the first large phase 3 trial. The first phase of the trial results show that the average difference between the duloxetine group and placebo was 0.073 (p=0.003), better than the reference research[36] using duloxetine for pain in diabetic neuropathy. Range for the difference in the average score of pain that FDA approved for diabetic neuropathy, fibromialgia, and osteoarthritis is 0.60-0.98. But in contrast, this comparation still not right, because the mechanisms in peripheral neuropathy induced by chemotherapy which cause by taxane and platinum regiments, are difference from others nerve injury. However this study showed clinically important change, consider that patients experiencing an improvement in pain severity during initial treatment dominated by using of duloxetine. A decrease in pain score itself are over minimally significance threshold (10%) that set by IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials, which mission is to develop consensus reviews and recommendations for improving the design, execution, and interpretation of clinical trials of treatments for pain).

The results of Smith et al.,[17] confirmed by Hirayama et al.,18 which randomized 34 patients in Japan. Patients were divided into two groups: Group A who receive duloxetine followed by VB12 and Group B who receive VB12 followed by duloxetine. Group A received duloxetine 20 mg/day at first week continued with 40 mg/day the next 3 weeks. Group B received VB12 1.5 mg/day for four weeks. Continued with the washout period 2-4 week, and then the treatment was exchange between 2 groups for another four weeks. They measure the pain and numbness every week using Visual Analog Scale. Obvious reductions seen in mean VAS score during the periods of duloxetine administration. These tended to decline 4 weeks after duloxetine administration. Duloxetine showed had significant differences for pain and numbness. Standard dosage of duloxetine in US and Japan are different based on duloxetine standard dosage for diabetic neuropathy (US higher than Japan).

Smith et al., study claimed to have a strengths on the design of the experiments that are randomized, prospective, using placebo control, and samples come from a wide geographical distribution.[17] However, the study also acknowledged to have weakness, which are that implementing a scale measuring pain not specifically trained to assess the level of pain in CIPN patients and based only on CTCAE standard practical guidance. But since standard CTCAE consistent with academic and community clinical practice, then the findings that are based on this standard are declared valid. Another substantial limitation is the lack of enough times for duloxetine treatment, which the proper times are more than 5 weeks.

Hirayama et al., study have strength there are homogeneity at patients characteristics.[18] This study said that no significant differences between groups in therapy types, median age, also ratio female and male. Limitation of these study are instead of using placebo as a comparator because ethical considerations, therefore using a VB12, that shown didn't have any effects on CIPN and only has a few side effects. But in the Hirayama study, shown some tendency for VB12 administration could improve numbness and pain, but the before and after difference are not significant.

Avan et al., examine the effectiveness of duloxetine in breast cancer patients who receive paclitaxel or docetaxel and experience TIPN (taxane-induced peripheral neuropathy) with age more than 18, neuropathy grade ≥ 1, and pain score ≥ 4 based on VAS.[19] The comparison between duloxetine and pregabalin with dosage 75 mg/day pregabalin for first week, followed by 75 mg twice a day for second until sixth weeks. Duloxetine given with dose 30 mg/day for first week, followed by 30 mg twice a day for second until sixth weeks. In this case pregabalin showed more significant than duloxetine to reduce pain. The QOL score for both groups did not significanly difference.

Table 1. Summary of study characteristic

Study	Year	Type of Study	Cancer Type	Chemotherapy regimen	Country	Sample size	Study duration	Comparator	Primary outcome	Adverse Events as Secondary Outcome
Smith, et al	2013	RCT	Various cancers	Paclitaxel, docetaxel, cisplatin, oxaliplatin	USA	231	14 weeks	Placebo	average pain by BPI	Yes
Hirayama, et al	2015	RCT	Various cancers	paclitaxel, oxaliplatin, vincristine, bortezomib	Japan	34	10-12 weeks	Vitamin B12	Change of pain and numbness by VAS score	Yes
Wang, et al	2017	open label - prospective	Breast cancer	Paclitaxel	Chinese	131	12 weeks	anti neurotoxicity drugs	FACT-Tax Scales	Yes
Avan, et al	2018	RCT	Breast cancer	paclitaxel or docetaxel	Iran	82	6 weeks	pregabalin	QOL, pain (EORTC QLQ)	Yes

*RCT-Randomized Control Trials; BPI-Brief Pain Inventory; VAS-Visual Analogue Scale; FACT-Tax-Functional Assessment of Cancer Therapy-Taxane; QOL-Quality Of Life; EORTC-QLQ- European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire

Table 2. Summary of study results

Study	Total Participants	Age, years	Sex, M/F	Duloxetine dosage	Comparator	Duration	Primary Outcome	Secondary Outcome
Smith, et al 2013	231 total Group A: 109, Duloxetine first Group B: 111, placebo first	30-75 A = 60 (mean) B = 59 (mean)	82/138 A = 38/71 B = 44/67	• 30mg/day (1st week) • 60mg/day (next 4 weeks)	Placebo	• Initial (1-5 weeks) • washout period (2 weeks) • cross over (8-12 weeks)	• Mean reducing average pain, group A 1.06 and group P 0.34, with p = 0.003 • RR (relative risk) group A for 30% pain decreasing = 1.96, 50% pain decreasing = 2.43	• Fatigue (7%) • Nausea (5%) • Insomnia (5%)
Hirayama, et al 2015	34 total Group A : 17, Duloxetine → Vitamin B12 Group B : 17, Vitamin B12 → Duloxetine	48-75 A = 61 (median) B = 64 (median)	17/17 A = 8/9 B = 9/8	• 20mg/day (1st week) • 40mg/day (next 3 weeks)	Vitamin B12	• 4 weeks • washout period (2-4 weeks) • cross over (4 weeks)	Hazard ratios duloxetine groups in initial treatment: • A 30% decreasing in pain were 0.40 and numbness duloxetine were 0.25 • A 50 % decreasing were 0.28 and 0.25, respectively	• Fatigue (17.6 %). • Insomnia • Somnolence • Nausea
Wang, et al 2017	102 total Group A : 53, duloxetine Group B : 49, control	A = 49 (43–53) B = 51 (43–57)	-	-	Anti-neurotoxicity drugs (NSAID, fish oil, Vit B)	12 weeks	The mean reducing pain score in duloxetine groups versus other-anti neurotoxicity drug groups are 3.89 and 2.10.	• Eye distention • Somnolence • Nausea • Dizziness • Constipation
Avan, et al 2018	82 total Group A : 40, Pregabalin Group B : 42, Duloxetine	29-72 A = 29-72 B = 30-71	-	• 30mg/day (1st week) • 30mg twice a day (until 6 week)	pregabalin	6-weeks	The mean score of pain significantly declined both in pregabalin and duloxetine group ($p < 0.001$)	Nausea & vomiting

*NSAID-Non Steroidal Anti-Inflammatory Drugs

Study	Hedge's g	Lower Limit	Upper Limit
Smith 2013	0.422	0.156	0.690
Hirayama 2015	0.603	-0.076	1.302
Wang 2017	0.204	-0.184	0.595
Avan 2018	-0.170	-0.604	0.264

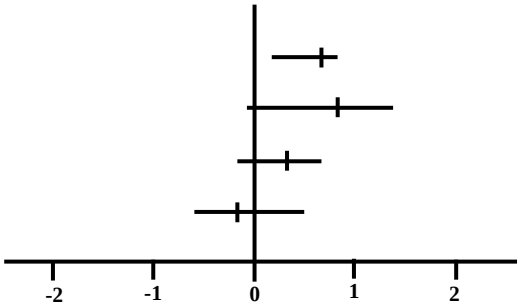

Figure 3. Forest plot

Same trials recently in China, with 102 breast cancer patient, median age is 50 years (range 25-60 years).[20] In these trial, duloxetine given orally 30 mg/day for the first 4 weeks and 60 mg/day for the next 8 weeks. The comparison is other neurotoxicity drugs with the same duration. Duloxetine shows a better results for reducing pain seen in FACT-Tax with median decrease is 4 (2-6) and the other drugs is 1 (0-4) with p = 0.005.

Secondary Outcomes (Adverse Effects)

Several things to note from the use of duloxetine related adverse effects is duloxetine could not be used in conjunction with medications are serotonin reuptake inhibitors for the process because there are an increasing risk of the ocurence of the syndrome serotonin.[39] Duloxetine also couldn't administrate together with substrate CYP P450 2D6 because duloxetine is a moderate inhibitor of the enzyme. It could lead to an increase in the concentration of serum drug substrate and related to toxicity.[40-43] The use of duloxetine with NSAID, warfarin, or both, might increase the risk of bleeding.[39,44] Duloxetine also inhibits the conversion of tamoxifen to endoxifen, active metabolits, related properties of an inhibitor CYP P450 2D6.[39,41,45,46]

All the adverse effects are summarized in table 3. Study in Japan showed that fatigue happen in 17,6% patients (6/34), and the others are nausea (3%), somnolence (2%), and insomnia (2%).18 Approved by Smith et al, that fatigue, insomnia, and nausea were the most common adverse effects happened, with presentase 7%, 5%, and 5% respectively.[17] Avan et al also confirmed nausea and vomiting was more common in patients that use duloxetine, different with pregabalin patients that more complain about somnolence and dizziness.[19] The other adverse effects added by Wang et al., such as constipation, dizziness, and eye distention.[20]

Table 3. Sumarry of adverse effects

Adverse Effects
Fatigue
Somnolence
Dizziness/Giddiness
Nausea vomiting
Constipation
Headache
Eye Distention
Dysgeusia

Discussion

Duloxetine is widely used and proved for the management of diabetic neuropathy (pain that caused by damage of the nerve in patients with diabetes).[16] The newest guideline about prevention and treatment of adult patients with cancer from ASCO (American Society of Clinical Oncology) also recommends the use of duloxetine for management of CIPN.15 The purpose of this study is to systematically review and determine the efficacy and safety of using duloxetine for management CIPN in particular for reducing the pain.

There are still a few direct evidence to support using drugs from adjuvant analgesics groups (e.g., antidepressants and anticonvulsants) in the CIPN setting, although many clinicians empirically use them based on other pain management principles.[35] The author of this article found 4 experimental study that assess the effects of using duloxetine for CIPN, but these 4 study has different tools to measure the outcome which include pain as one of them.[17-20] Nowdays, there is no consensus exists regarding which of these measures are the best for assessing the outcomes of CIPN treatment. This lack of standardized primary outcome measurements necessitates further studies that characterize and separate CIPN-related pain from other sensory symptoms; using standard outcome measures will help to determine the best outcome measure for future CIPN treatment trials.

There are some previous positive trials of using duloxetine for decreasing pain scores in the treatment of neuropathic pain resulting from chemotherapy agent. Smith and colleagues (2013) concluded that compared to placebo, using duloxetine for five weeks showed a clinically and statistically pain improvement.[17] After four weeks treatment of duloxetine shown a lower mean Visual Analog Scale (VAS), compared to the one who get Vitamin B12 for treatment.18 The meaningful reduce from the mean Visual Analog Scale (VAS) scores shown during the duloxetine treatment in Japan patients.18 Using duloxetine for decreasing a pain intensity also seen in open label prospective experiment to breast cancer patients in China.[20] This study shown a better pain intensity after get duloxetine for 12 weeks, proven by Functional Assessment of Cancer Therapy-Taxane (FACT-Tax) pain decrease 4 in duloxetine group and 1 in control group. Other studies also observed significant improvement in emotional functioning, pain, global health, and QOL domains of EORTC QLQ C-30 questionnaire in duloxetine group. Duloxetine was

successfully used for patients with cancer who have mood disorder, and it was associated with improvement in global QOL, especially in emotional functioning, pain, global health, and QOL subscales.[19]

From the meta-analysis results we could see that in the forest plot (figure 3), study by Avan, et al had a tendency to stay away from duloxetine, which is probably because the study conducted by Avan used pregabalin as a comparison instead of placebo. As we know, pregabalin showed more effectiveness than duloxetine to treat peripheral neuropathy. Meanwhile the opposite from Avan, the only study that supports duloxetine completely is study by Smith, et al. Seen by the line that represent Smith on the forest plot, the line does not touch the line 0. This is because Smith, et al study was the only study in this review which used placebo as a comparison.

The increase in the number of occurrence of adverse events is an issue that should be resolved when adding a drug to treat a chemotherapy-induced peripheral neuropathy. Therefore, it is important to report adverse events as secondary outcomes when evaluating the efficacy and safety of the use of duloxetine for CIPN. Adverse effects of duloxetine were very well tolerated in a population of patients with breast cancer in China.[20] The adverse effects were found are somnolence, constipation, dizzined, eye distention, and nausea. According to Wang et al., to decrease the possibility to have nausea and vomiting, patients should swallowing duloxetine (capsule form) after meals also without chewing and crushing.[20] These are consistent with Avan et al., that the adverse effects were mild and well-tolerated.[19] In the study by Smith et al., patients who discontinued because of the adverse effects are higher on groups that are used duloxetine as their first treatment compared to the placebo groups (11% versus 1%).[17] Beside that, Smith also reported the other adverse effects that are nausea, insomnia and fatigue. Same with Smith, in the study by Hirayama five patients was discontinued because of fatigue.18 Fatigue was the most frequent adverse effects according to Hirayama, seen in 6/34 patients (17.6%).

Conclusion

There are some limitations about this study, one of them was the included study in this review was only 4, due to lack of RCT in this population. Resulting there is still not enough evidence to evaluate the effects of duloxetine for the management of CIPN. Randomized Control Trials which include a large number of participant was needed in the future. We could conclude that for the treatment of CIPN, duloxetine is a great option, especially for reducing neuropathic pain. But in comparison with pregabalin showed less effective. The adverse effects of duloxetine a majority are mild and well-tolerated, but clinicians need to pay attention when give duloxetine to elderly people, maybe an adjusting dose should be considered.

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Conflict of Interest

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