

REVIEW PAPER

A Review of The Use of Mirtazapine in Cancer Patients

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Abstract

Introduction: Cancer patients often have concurrent physical and psychological symptoms. These problems may become barriers towards the healing process. Antidepressants seem to be beneficial for the purpose of palliative care in this type of patients. One of the useful medications is mirtazapine, which is known as noradrenergic and specific serotonergic antidepressant (NaSSA). This paper examines the use of mirtazapine in physical and psychological symptoms of cancer patients. **Methods:** Literature search was done on PubMed (from inception to January 2017) by matching the key terms: 'noradrenergic and specific serotonergic antidepressants' or 'NaSSA' 'mirtazapine' AND 'cancer' or 'oncol*' or 'malignancy' or 'carcinoma'. Eligible papers were screened at the title and abstract level. Various types of study included in this review, according to certain criteria. Additional papers were also identified by screening of reference lists. **Results:** A total of twelve papers were reviewed and summarized. Positive findings obtained for the use of mirtazapine in cancer patients associated with various symptoms, including depression, anxiety, cachexia, nausea, hot flashes, and pruritus. Some rare side effects are reported, including constipation, myalgia sedation, dry mouth, stimulation of appetite and weight gain. **Conclusion:** Mirtazapine has the potential to be beneficial for cancer patients suffering from these physical and psychological symptoms. However, more research studies with sufficient power are warranted to validate the findings.

Keywords: Cancer, Antidepressant, Mirtazapine, Depression, Anxiety, Nausea

Introduction

Mirtazapine is considered as one of the

recommended antidepressant for the treatment of Major Depressive Disorder (MDD), in addition to other classification of

antidepressants, which known as selective serotonin reuptake inhibitors (SSRIs) [1, 2]. In comparison to SSRIs and other antidepressants, mirtazapine has special pharmacological profiles, which include antagonistic effects on α_2 -adrenaline, histamine H_1 and serotonin $5-HT_{2A}$ receptors [3]. Additionally, it is said to be effective for anxiety, due to antagonistic activity in the $5-HT_{2c}$ receptor [4]. Onset of action for mirtazapine is reported to be faster than SSRIs [5, 6]. A recent study reported that mirtazapine may reduce benzodiazepine use in patients with MDD [7].

Cancer patients are commonly associated with depressive spectrum disorder, with the prevalence is higher compared to normal population. According to a paper [8], the highest range can be up to 58%. Depression in cancer patients may be associated with nausea and sleep disturbance [9]. Nausea could be from treatment side-effects of chemotherapy, which is worsen by occurrence of vomiting and frequent urination [10]. Then, sleep may be disturbed by these side effects, in addition to the psychiatric problem itself; making sleep disturbance has become the most frequent symptoms experienced by cancer patients [11, 12].

In treating cancer patients with antidepressant, several factors should be taken into consideration. Even though SSRIs had become the first line treatment for depression in general population, cancer patients may have different situation. Together with SSRIs, serotonin norepinephrine re-uptake inhibitors (SNRIs) show similar issue of limited use in cancer patients due to precipitation of sleep disturbance and nausea, as a result of agonist effects on $5-HT_2$ and $5-HT_3$ receptors [9, 13].

Therefore, mirtazapine has been the treatment of choice for cancer patients, due to its antagonistic effects on $5-HT_2$ and $5-HT_3$ receptors [14]. Among the benefits of mirtazapine for cancer patients with depressive symptoms include the ability to control nausea and vomiting [15], help sleep continuity [16], as well as increase appetite that may help anorexic patients to gain weight [14].

In view of these benefits, mirtazapine should be prioritized for this type of patients. The depressive symptoms may be controlled, while other concomitant conditions are taken into consideration. However, insufficient evidences were found in the literature to support the practice of this medicine. Therefore, this paper aims to review the use of mirtazapine in cancer patients, focusing on palliative aspect of the patient care.

Methods

To identify the studies on the use of mirtazapine in cancer, we conducted a search on PubMed (from inception to January 2017) by matching the key terms: 'noradrenergic and specific serotonergic antidepressants' or 'NaSSA' 'mirtazapine' AND 'cancer' or 'oncol*' or 'malignancy' or 'carcinoma'. We included controlled trials, review article, meta-analysis, editorial, commentary, correspondence and letter to editor published fully in peer-reviewed journal and written in English. Reference lists from the selected relevant articles were searched for additional trial or studies. For the purposes of discussion, the main outcomes of the included studies were extracted and tabulated.

Results

A randomized controlled trial, a cohort study and a case series were identified in studying

the use of mirtazapine for depression in cancer patients. There were also three cohort studies and a case series reported the use of mirtazapine for symptoms associated with cancer such as cachexia, anorexia, nausea, insomnia, hot flush and pruritus.

A randomized controlled trial from Turkey [17] was conducted to compare the effectiveness of mirtazapine and imipramine for the psychiatric problems of depression and anxiety as well as distressing symptoms of cancer patients, such as nausea, vomiting, pain, sleep disturbances and appetite loss. The interventions groups consist of mirtazapine (n = 20) and imipramine (n = 13), while control group is placebo (n = 20) in 6 weeks' treatment duration for patients with mixed types of cancer.

The findings show significant changes on the mean total scores of anxiety and depression in mirtazapine group, instead of imipramine group and placebo group. Similar to these psychiatric problems, sleep disturbance also can be controlled by using mirtazapine. In terms of appetite loss, nausea, vomiting and pain, there were no significant differences among the three groups.

However, this study [17] has limitation of not using effective dosages of medications for the study subjects, as well as using mixed type of cancer patients. Different inclusion criteria in terms of cancer type and stages may influence the results. Therefore, more systematic researches by using improved criteria are warranted.

Next, we included a cohort study related to the treatment of depression in cancer patients. The study [18], which had 6 months treatment duration, used prospective, naturalistic open label design. Similar to previous study, it included all stages of

cancer patients. Even though significant reduction in depression scores as measured by 17-item Hamilton Rating Scale for Depression (HAM-D-17) had been observed, the small sample size (n = 21) had limited the generalization of this study conclusion with other settings.

Besides, another paper [19] had reported case series on mirtazapine for the depression and nausea treatment in breast and gynecological oncology. According to this author, during the year of 2000, 19 out of 20 oncology patients had successfully been treated with mirtazapine. The age ranges for those women are from 36 to 74 years old. All of them were diagnosed with gynecological or breast cancer and also have mood, anxiety or adjustment disorders. They also experienced a reduction in nausea symptoms, improvement in sleep continuity, decrement in depressive symptoms, and increment in appetite.

A letter to editor [20] had reported regarding the use of mirtazapine for depression and comorbidities among older patients with cancer. There are several studies that have provided evidences to improve comorbid symptoms associated, such as cancer cachexia, as well as nausea and vomiting among elderly cancer patients. Despite of rare adverse effects which include reversible neutropenia, drowsiness at low doses and constipation, mirtazapine had fewer gastrointestinal side effects (nausea, vomiting and diarrhea), if compared to SSRIs. Another benefit of mirtazapine is that the lower price than ondansetron, the most widely used antiemetics for cancer.

Furthermore, we found a review article [21] related to the claim of mirtazapine, to be an alternative to ondansetron in producing antinausea effects. Mirtazapine had been suggested as the first-line options in treating

nausea induced by chemotherapy and cancer itself. Besides having superior or equal efficacy in the control of nausea and vomiting in comparison to ondansetron, mirtazapine has longer half-life.

Besides, two letters to editors have been found, related to mirtazapine usefulness in the treatment of nausea in cancer patients. The first letter [22], mentioned that instead of binding to re-uptake protein as seen in fluoxetine, mirtazapine binds to the 5HT₃ receptor as similar as binding site for ondansetron. Therefore, mirtazapine can

produce anti-nausea effect, improve appetite, and weight gain as a result of its side effects. This is important since weight loss is a common problem for cancer patients who are under chemotherapy regimen.

The second letter [23], mentioned that, apart from the reduction of nausea in cancer patients, mirtazapine can also ameliorate cancer cachexia. As a result of increase food intake after administration of mirtazapine, weight will be gained. At the same time, significant improvement in quality of life can be obtained.

Table 1. Summary of included papers of mirtazapine for cancer patients

First author & Year (Ref. No.)	Title	Type of Paper	Description of findings
Cankurtaran ES, et al. 2008 (17)	Mirtazapine improves sleep and lowers anxiety and depression in cancer patients: superiority over imipramine.	Randomized Controlled Trial (RCT)	Significant changes on the mean total scores of anxiety and depression in mirtazapine group, instead of imipramine group and placebo group.
Ersoy MA, et al. 2008 (18)	An open-label long-term naturalistic study of mirtazapine treatment for depression in cancer patients.	Cohort Study	Significant reduction in depression scores as measured by 17-item Hamilton Rating Scale for Depression (HAM-D-17) had been observed.
Thompson DS, 2000 (19)	Mirtazapine for the treatment of depression and nausea in breast and gynecological oncology.	Case Series	19 out of 20 oncology patients had successfully been treated with mirtazapine, during the year of 2000.
Raji MA, et al. 2007 (20)	Mirtazapine for depression and comorbidities in older patients with cancer.	Letter to Editor	Several studies have provided evidences to improve comorbid symptoms associated, such as cancer cachexia, as well as nausea and vomiting among elderly cancer patients.
Kast RE, et al. 2007 (21)	Cancer chemotherapy and cachexia: mirtazapine and olanzapine are 5-HT ₃ antagonists with good anti-nausea effects.	Review Paper	Mirtazapine had been suggested as the first-line options in treating nausea induced by chemotherapy and cancer itself, due to its superior or equal efficacy in the control of nausea and vomiting in comparison to ondansetron.

Kast R, 2001 (22)	Mirtazapine may be useful in treating nausea and insomnia of cancer chemotherapy.	Letter to Editor	Mirtazapine can produce antinausea effect, improve appetite, and weight gain, due to the binding with 5HT ₃ receptor as similar as binding site for ondansetron.
Kapoor S, 2013 (23)	Additional advantages of mirtazapine therapy in cancer patients: beyond its role as an antidepressant.	Letter to Editor	Apart from the reduction of nausea in cancer patients, mirtazapine can also ameliorate cancer cachexia as well as improve weight gain.
Jiang SM, et al. 2012 (24)	Intervention of mirtazapine on gemcitabine-induced mild cachexia in nude mice with pancreatic carcinoma xenografts.	Animal Study	The results showed intervention mice were eating more food than control.
Riechelmann RP, et al. 2009 (25)	Phase II trial of mirtazapine for cancer-related cachexia and anorexia.	Cohort Study	Mirtazapine is a promising agent for cancer-related cachexia and anorexia (CRCA).
Kim SW, et al. 2008 (9)	Effectiveness of mirtazapine for nausea and insomnia in cancer patients with depression.	Cohort Study	Mirtazapine could be used as an effective treatment option in managing cancer patients with nausea and sleep disturbance.
Biglia N, et al. 2007 (26)	Mirtazapine for the treatment of hot flushes in breast cancer survivors: a prospective pilot trial	Cohort Study	Hot flushes reduction had been observed after 12 weeks treatment of mirtazapine 30 mg per day among those women with the history of cancer.
Lee JJ, et al. 2016 (27)	Effective use of mirtazapine for refractory pruritus associated with carcinoma en cuirasse.	Case Report	Cancer patient who had pruritus with cutaneous infiltration may get benefit from the use of mirtazapine for the palliative relief.

We found an animal study [24] related to this issue. Gemcitabine had been used on nude mice for seven days to produce mild cachexia model. Therefore, mirtazapine can be used to test the hypothesis. The results showed intervention mice were eating more food than control. However, this animal study result should be supported by clinical test in human study.

Therefore, we include two cohort studies related to the effectiveness of mirtazapine in treating cachexia and nausea. First cohort study [25] mentioned that mirtazapine is a promising agent for cancer-related cachexia and anorexia (CRCA). This was a phase II trial among nondepressed patients with CRCA, treated with mirtazapine until 8 weeks' study duration. Even though the results are encouraging, interpretation should consider the small sample size ($n = 17$) and single site study only.

Then, second cohort study [9] mentioned that mirtazapine could be used as an effective treatment option in managing cancer patients with nausea and sleep disturbance. This cohort study was done for 4 weeks with the outcomes were measured at baseline, days 1, 3, 5, 7, 14, and 28. However, the positive findings should also be treated with cautions since this study lacks of control group.

Hot flashes (HF) may become a comorbid symptoms associated with cancer patients. A prospective pilot trial [26] using mirtazapine for HF treatment had been done on breast cancer survivors. HF reduction had been observed after 12 weeks treatment of mirtazapine 30 mg per day among those women. However, data from this preliminary study need to be justified in a larger randomized controlled-trial (RCT).

A case report had been published in 2016

[27], stating that cancer patient who had pruritus with cutaneous infiltration may get benefit from the use of mirtazapine for the palliative relief. Despite of other systemic and topical therapies for pruritus management, oral mirtazapine had successfully managed the patient's condition that had a severe treatment refractory pruritus associated with carcinoma en cuirasse. The dosage of mirtazapine used in these patients was 7.5 mg orally nightly and finally, increased to 15 mg orally daily.

Discussion

In the current review, we found that mirtazapine had several contributions in treating psychological and physical symptoms associated with cancer patients. Mirtazapine acts by blocking the serotonin (5-HT) receptors, specifically at 5-HT₂ and 5-HT₃ subtypes, in addition to its potent antagonist of central 2 α -adrenergic autoreceptors. Furthermore, it will also enhance the activity of 5-HT₁ postsynaptic receptors, and eventually increase both noradrenergic and serotonergic transmission, contributing to the widely used term of noradrenergic and specific serotonergic antidepressant (NaSSA) [20, 28].

The most beneficial characteristic of mirtazapine is the absence of exacerbation of nausea or suppression of appetite, which are the most commonly side effects reported for other antidepressant medications¹⁹. Furthermore, mirtazapine can potentially be a cost-effective antiemesis therapy, since it is cheaper than ondansetron, the widely used antiemesis, currently.

On the other hand, hot flashes (HF) in cancer patients, especially women, can also be reduced by using mirtazapine. This may be due to its mechanism that will increase central serotonergic and noradrenergic

activity as a result of antagonistic effects at alpha 2 receptors along the central presynaptic membrane. Additionally, mirtazapine inhibits other receptors such as histamine, that is commonly located at the postsynaptic [26]. Once daily dosing of mirtazapine is a convenience choice for women, due to long half-life (20 to 40 hours) with delayed clearance in women (37 hours), if compared to men (26 hours) [29].

Pruritus in cancer patients may be reduced by mirtazapine, due to its unique mechanisms of action as current hypotheses supported the view of antagonism effects in various receptors, including serotonin (5-HT₂ & 5-HT₃), histamine (H1) and α 2-adrenergic. However, precise mechanism of pruritus alleviation by mirtazapine has yet to be defined [27].

Nevertheless, mirtazapine has some side effects. One of them is myalgia, as mentioned in a study [19]. However, it seems to be not significant due to rare occurrence, with 2% incidence rate from short-term controlled studies. Another paper [14] reported several side effects of mirtazapine, including sedation, dry mouth, stimulation of appetite and weight gain. Similarly, these side effects are quite rare and some of them are desirable.

Mirtazapine shows a favourable safety profile, with a wide therapeutic index, and has less inhibitory effect on cytochrome P450 enzymes, contributing to unlikely of drug interactions to occur [14, 30]. However, alcohol and benzodiazepine should be avoided when administering mirtazapine, since the sedation effect may get worsened [30].

Conclusion

In a nutshell, it is reported that mirtazapine

has potential to be a useful medication for cancer patients suffering from depression and anxiety symptoms with concurrent problems of nausea, cachexia, sleep disturbances, low appetite, hot flashes, or pruritus. However, more research studies with sufficient power are warranted to validate the use of mirtazapine in cancer patients for treating these physical and psychological symptoms.

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