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Original Research Paper

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OFF-LABEL USE OF MIRTAZAPINE FOR MANAGEMENT OF POLYSYMPTOMATOLOGY IN ADVANCED CANCER PATIENTS—A CASE SERIES

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ABSTRACT Patients suffering with advanced cancer are polysymptomatic, thus for relieving symptoms, they generally receive many medications. Frequently seen symptoms include loss of weight, loss of appetite, anorexia, depression, nausea, vomiting and delirium. Polymedication raises the chances of interactions of drug and its side effects in case of this multimorbid and frail population. Mirtazapine is increasingly utilized as an off-label treatment of poly-symptoms like loss of appetite, anxiety, depression, nausea and insomnia. The following case reports will highlight the potential benefit of off-label mirtazapine use for polysymptomatology management in advanced cancer patients.

KEYWORDS : mirtazapine, poly-symptomatology, advanced cancer,

INTRODUCTION:

Advanced cancer is defined as the type of cancer that is implausible to get cured or prevented after treatment. This type of cancer is also known as the terminal or end-stage cancer (1,2). Such patients are managed using nonsurgical modalities like best supportive care, concurrent chemoradiation, radical and palliative radiation. The nonsurgical treatment modalities attain a lasting cure rarely. Patients suffering with advanced cancer are polysymptomatic, thus for relieving symptoms, they generally receive many medications (3). Frequently seen symptoms include loss of weight, anorexia, depression, and delirium. Polymedication rises the chances of interactions of drug and its side effects in case of this multimorbid and frail population (4). Patients with advanced cancer typically require multiple drugs to relieve their symptoms because they are polysymptomatic.

Mirtazapine is a noradrenergic and selective serotonergic antidepressant that works by inhibiting 5-HT2 and 5-HT3 receptors and opposing adrenergic alpha2-autoreceptors and heteroreceptors. Mirtazapine does block H_1 and $5\text{-}HT_{2c}$ receptors which lead to sedation and increased appetite, respectively (5). Mirtazapine has aggravating appetite-stimulating, gastric emptying, and improvement of quality of sleep or anxiolytic effects (6). It can be considered as highly helpful antiemetic agent for increasing the whole Quality of Life after chemotherapy. More clinical experience and research is required to explain their role in the advanced cancer palliation.

Case report:

Advanced cancer patients attending palliative care department at tertiary care centre, After obtaining written informed consent, the case report was performed on four patients aged >18 years with suffering from an histologically diagnosed advanced cancer (Cancer with Metastasis), Patients with a complain of multiple symptoms like- loss of body weight, decrease appetite, anxiety, depression, insomnia, nausea and vomiting were included in the study.

Pregnant and lactating female, Known history of hypersensitive to mirtazapine drugs, ryles tube feeding patients, Severe renal impairment, Severe liver impairment, Significant disorder of bone marrow, Cardiac conduction defect, EKG changes suggestive of cardiac disease and QTc prolongation, patient taking antipsychotic, sedative-psychotropic drug, atropine and its substitute, non co-operative patient, patient are not giving written informed consent for this case study were also excluded from the study.

As per study protocol, all the patients were interviewed, briefed and counseled about the drugs. Previous medication history, clinical examination and investigations were reviewed and vitals of all the patients were recorded. All the selected patients were prescribed Tablet Mirtazapine 15 mg/day orally at night once per day for 4 weeks and provided study questionnaire - Edmonton Symptom Assessment Scale (ESAS) for assess to symptoms. Patient's ESAS score for appetite, depression, anxiety, sleep and nausea was measured at baseline and at 4th weeks of follow-up period (Table).

Patient 1: A 42 year male patient has been diagnosed with carcinoma pancreases with liver metastasis. Pain relief adequate with Tablet Morphine 10 mg orally every four hourly, Tablet Paracetamol 650 mg orally three times a day, Tablet Gabapentin 300 mg orally once a day, Tablet Bisacodyl 10 mg orally at night and Capsule Omeprazole 20 mg orally. His latest laboratory findings are serum urea-42mg/dl, serum creatinine-0.8mg/dl, SGOT-31U/L, SGPT-28U/L, serum bilirubin-0.3mg/dl, hemoglobin-9.8g/dl.

Patient 2: A 36 year male patient has been diagnosed with carcinoma lung left side with bone metastasis, his Pain relief adequate with Tablet Morphine 20 mg orally every four hourly, Tablet Etoricoxib 90 mg orally once a day, Tablet Gabapentin 300 mg orally once a day, Tablet Bisacodyl 10 mg orally at night and Capsule Omeprazole 20 mg orally to cover other neuropathic pain and constipation in this patient. His latest laboratory findings are serum urea-34mg/dl, serum creatinine-0.9mg/dl, SGOT-26U/L, SGPT-18U/L, serum bilirubin-0.7mg/dl, hemoglobin-10.1g/dl.

Patient 3: A 32 year female patient has been diagnosed with carcinoma breast, post operative case, her Pain relief adequate with Tablet Morphine 5 mg orally every four hourly, Tablet Paracetamol 650 mg orally three times a day, Tablet Pregabalin 75 mg orally twice a day, Tablet Bisacodyl 10 mg orally at night and Capsule Omeprazole 20 mg orally. Her latest laboratory findings are serum urea-37mg/dl, serum creatinine-0.8mg/dl, SGOT-24U/L, SGPT-26U/L, serum bilirubin-0.9mg/dl, hemoglobin-10.3g/dl.

Patient 4: A 27 year male patient has been diagnosed with carcinoma buccal mucosa, his Pain relief adequate with Tablet Morphine 10 mg orally every four hourly, Tablet Etoricoxib 90 mg orally once a day, Tablet Pregabalin 75 mg orally twice a day, Tablet Bisacodyl 10 mg orally at night and Capsule Omeprazole 20 mg orally. His latest laboratory findings are serum urea-32mg/dl, serum creatinine-0.9mg/dl, SGOT-24U/L, SGPT-18U/L, serum bilirubin-0.6mg/dl, hemoglobin-10.5g/dl.

Patients	ESAS SCORE									
	Appetite		Depression		Anxiety		Sleep		Nausea	
	At baseline	At 4th week	At baseline	At 4th week	At baseline	At 4th week	At baseline	At 4th week	At baseline	At 4th week
Case 1	6	2	5	4	6	3	7	2	4	3
Case 2	8	3	7	4	5	4	6	3	5	2
Case 3	6	3	6	2	7	3	5	4	3	2
Case 4	7	4	5	3	5	2	6	2	6	3

DISCUSSION:

The aging population and increasing prevalence of cancer with age may lead us to expect an increase in the number of patients undergoing polypharmacy therapy, both for advanced cancer and palliative care (7). This presents a risk to these patients' safety as well as their quality of life. Better managing the aging cancer population requires evaluating medications that lower the risk of polypharmacy while also improving quality of life and treating a range of symptoms (8). It's challenging to manage its many distressing symptoms. Thus, finding a medication that lessens a variety of symptoms would be helpful in preventing polypharmacy.

Off-label usage of mirtazapine for the management of polysymptomatology, such as anxiety, sleeplessness, and anorexia in cancer patients, is growing.

Arrieta O et al (9) conducted a study to Mirtazapine as Appetite Stimulant in Patients with Non–Small Cell Lung Cancer and Anorexia. They observed that there was no significant difference in the appetite scores for patients who were treated with mirtazapine or placebo, but they found that mirtazapine group showed a significant rise in energy intake, mainly in intake of fat, which is a good source of energy. They stated that when mirtazapine is added in the management of patients having advanced cancer and anorexia, it generally help patients to gain energy and improve the health-associated quality of life, mainly cognitive and emotional functioning. **Watanabe N et al (10)** conducted a study to Mirtazapine versus other antidepressive agents for depression. They assessed the studies on the acceptability and efficacy of mirtazapine as compared with other antidepressive agents for managing the acute-phase of major depression in adults. They concluded that Mirtazapine was more likely to cause gain in the weight or rise in the appetite and somnolence. **Schutters SI et al (11)** conducted a study to Mirtazapine in generalized social anxiety disorder. They observed that investigated the tolerability and efficacy of mirtazapine in a generalized social anxiety disorder. They concluded that mirtazapine (30-45 mg/day) failed to be effectual in the comprehensive social anxiety disorder.

Mirtazapine can be treating multiple symptoms because of its effects on appetite stimulate and weight gain. Given that malnutrition shortens the life expectancy of patients with advanced cancer and is a source of treatment intolerance, the adverse effects of mirtazapine may be of great importance. For these reasons, mirtazapine might be the better choice when treating cancer patients with numerous symptoms and lowering polypharmacy.

CONCLUSIONS:

Mirtazapine is increasingly prescribed to cancer patients for off-label indications including the management of anxiety, nausea, insomnia, and appetite stimulation. More study is needed to evaluating off-label use of mirtazapine and other drugs for palliation of symptoms in cancer patients who are often frail and susceptible to adverse events particularly in the advanced stages of illness. In future there is a need to conduct single or multicentric studies, having a large sample size with long follow up period using even better scales, to get more authentic, conclusive and accurate results.

Declaration of patient consent:

This case study done after the all appropriate consent given by patients. In the form, the patients have been given consent for his/her clinical information to be reported in the publication journal.

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