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Mirtazapine: An Antidepressant for Treating Chronic, Refractory Nausea and Vomiting in a Patient With Metastatic Sarcoma Receiving Palliative Care: A Case Report

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ABSTRACT

Managing chronic, refractory nausea and vomiting in advanced cancer patients is challenging, especially when unrelated to cancer treatment. Mirtazapine, a tetracyclic antidepressant, effectively alleviates these symptoms, improving quality of life. It offers a promising palliative care alternative, addressing multiple symptoms and reducing polypharmacy, thereby enhancing patient satisfaction.

JEL Classification: Oncology

1 | Introduction

Nausea and vomiting (N&V), are prevalent distressing symptoms with incidence rates ranging from 40% to 70% in advanced cancer [1]. These symptoms may arise from treatment modalities such as chemotherapy, radiation, or surgery, or they may occur independently of cancer treatment [2]. N&V induced by antineoplastic agents or radiation therapy should be anticipated and managed following antiemetic guidelines, such as the ASCO antiemetic guideline [3].

A challenging clinical issue in cancer patients is the occurrence of "chronic N&V" which is unrelated to recent chemotherapy (ChT) or radiation treatment and affects 20%–60% of patients at some stage during the progression of their cancer [4, 5]. These cases involve ongoing N&V for weeks after treatment completion, often with unclear underlying causes [2]. Due to limited trial data on the use of antiemetics in these patients, management is currently predominantly empirical, relying on individual experiences and case studies [2, 6, 7].

Based on existing studies, various pharmacological treatments have been recommended, including prokinetics (e.g., metoclopramide, domperidone), antiemetics (such as ondansetron, promethazine), corticosteroids, antipsychotics (e.g., haloperidol, olanzapine), cannabinoids, and mirtazapine [4, 8–12].

This report describes the case of an adult patient presenting with chronic N&V that is also refractory to standard antiemetic treatments; however, a significant response to mirtazapine was demonstrated.

2 | Case Presentation

A 29-year-old man with a confirmed diagnosis of metastatic pelvic sarcoma was referred to the palliative clinic for the management of persistent N&V. The onset of symptoms coincided with the initiation of radiotherapy (RT) aimed at reducing the size of the abdominal mass. Despite the completion of the RT courses, the symptoms persisted. The patient reported

postprandial discomfort, anorexia, and N&V that began approximately 5 min after consuming solid food, with an intensity of 8/10 on the Numeric Rating Scale (NRS). Notably, there were no instances of insomnia or constipation associated with these symptoms. The patient expressed that his symptoms were interfering with his social activities and overall mood, and moderate depressive symptoms were revealed by the Hospital Anxiety and Depression Scale (HADS).

Physical examination revealed slight abdominal distention and a firm, non-tender mass approximately 6 cm in size in the right lower quadrant. Bowel sounds were normal, and there was no ascites. Abdominal ultrasonography showed a subcapsular liver metastasis measuring 31 × 23 mm in the right lobe and a hypoechoic mass measuring 32 × 22 mm in the liver hilum.

3 | Methods

Following a thorough assessment, an abdominal CT scan with and without contrast was performed. The scan revealed a mass measuring 59 × 49 mm at the level of the right lower pole of the kidney and another mass measuring 48 × 69 mm on the right side of the pelvis. The bowel and stomach appeared normal in both caliber and wall thickness, with no evidence of obstruction. Importantly, there was no evidence of peritoneal carcinomatosis.

Following the correction of dehydration and electrolyte imbalances, pharmacological treatment commenced with metoclopramide (total daily dose [TDD] titrated up to 60 mg), which did not improve the patient's symptoms. Subsequently, ondansetron (TDD 24 mg) was administered as the second antiemetic, but without improvement. Chlorpromazine was then initiated without yielding a response. To manage the persistent and refractory nature of the N&V despite standard antiemetic therapy and titration, the patient was admitted to the palliative care unit. Cannabinoid was the next pharmacological treatment initiated based on its established antiemetic properties. Although the patient was discharged with cannabidiol (CBD) drops twice daily, the symptoms recurred 2 days later. Subsequently, a regimen of mirtazapine at a known antiemetic dose (7.5 mg orally disintegrating tablet twice daily) was initiated in an outpatient setting.

Ethical Consideration: Written informed consent was obtained from the patient for the publication of this case report.

4 | Results (Outcome and Follow-Up)

The following day, the patient subjectively reported a 50% reduction in N&V (Figure 1). During the next visit, the patient complained of daytime drowsiness. To reduce the excessive drowsiness induced by mirtazapine, the dosage was adjusted to 7.5 mg per day, administered in the evening. After a 10-day follow-up, the patient reported the cessation of N&V, along with notable improvements in appetite and depressive symptoms.

5 | Discussion

The presented case reports the successful use of mirtazapine in a young patient with metastatic sarcoma, contributing to the limited existing data on its efficacy for managing chronic N&V coinciding with RT that persisted after the completion of the RT courses. Although previous studies indicate that patients may experience persistent episodes of N&V to a reduced degree weeks after abdominal, thoracic, and lumbosacral spine RT, the intensity of the symptoms did not decrease 2 weeks after the end of the RT courses [2, 13]. It appears that there are other etiologies, in addition to RT, that may be causing N&V in this case. The etiology of N&V in advanced cancer patients, independent of cancer treatment (ChT/RT), is multifactorial, with prominent factors including medication effects (e.g., opioids, anti-inflammatories, antidepressants, antibiotics), delayed gastric emptying, mechanical bowel obstruction, organ dysfunction (hepatic, renal), increased intracranial pressure, vestibular dysfunction, metabolic imbalances (e.g., hyponatremia, hypercalcemia), and cortical manifestations such as anxiety and depression [2, 4, 14]. The multifactorial etiology leads difficulties in treatment, despite most guidelines recommending antiemetic therapy based on an understanding

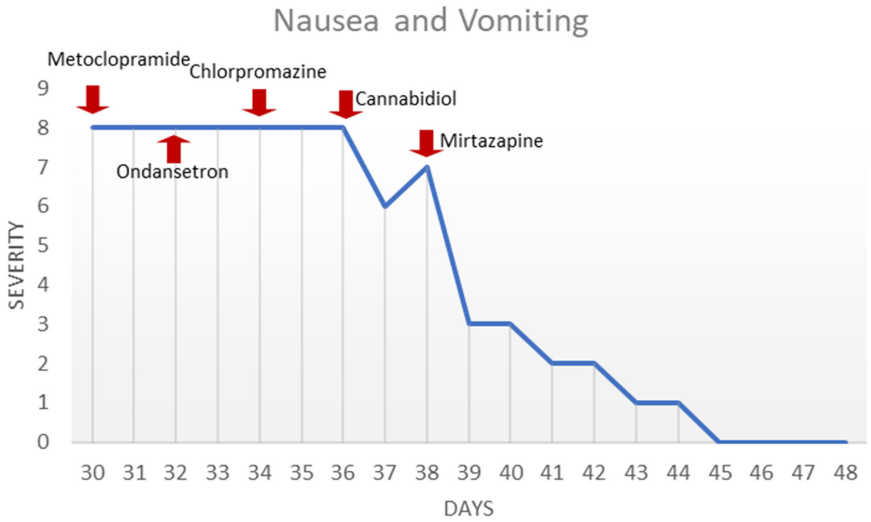

FIGURE 1 | Daily severity of nausea and vomiting following RT initiation and pharmacological treatment effects.

of the pathophysiological pathways implicated in the vomiting process and the specific receptors/neurotransmitters involved [3, 7]. Since standard monotherapy was ineffective in the presented case despite titration, and the N&V persisted, second-line antiemetics (e.g., cannabinoids, Mirtazapine) were added in accordance with guideline recommendations [3, 7, 15].

After starting cannabinoid tincture, despite observing an initial partial response, the patient experienced ongoing N&V and significant food intolerance. It must be noted that the main cannabinoids include delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC acts as an analgesic, muscle relaxant, antiemetic, appetite stimulator, and psychoactive agent, while CBD has demonstrated anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, antioxidant, and antipsychotic properties [14, 16]. CBD drops were prescribed for the patient since it was the only available cannabinoid. Consequently, in the absence of THC and its antiemetic effect, the anxiolytic effect of CBD likely led to partial improvement in the first few days of medication initiation. Mirtazapine was the next drug prescribed to the patient.

Mirtazapine, classified as a tetracyclic antidepressant (TeCA) and approved by the US FDA in 1996 for the management of major depressive disorder, is also used off-label for conditions such as insomnia, N&V, panic disorder, social anxiety disorder, fibromyalgia, post-traumatic stress disorder, and hot flashes [17, 18]. Its primary mechanism of action involves the antagonism of presynaptic α2 adrenergic receptors, leading to increased release of serotonin and norepinephrine. Additionally, it inhibits histamine (H1) and serotonin (5HT2A, 5HT2C, and 5HT3) receptors while activating 5HT1A receptors in both the peripheral and central nervous systems. Activation of 5HT1A receptors is thought to underlie its antidepressant and anxiolytic properties, while the blocking of H1, 5HT2A, and 5HT2C receptors also plays a role in some of its anxiolytic and sedative effects [9, 19, 20]. The currently recommended starting dose for mirtazapine is 15 mg per day [8, 19].

According to previous studies, behavioral causes are one of the proposed etiologies unrelated to the treatment of N&V [2, 4]. Despite the high prevalence of depressive disorders among patients with advanced cancer, it is often unrecognized, leading to reduced functional status, lower treatment adherence, and prolonged hospitalizations [21]. Not only does it affect the intensity of physical symptoms such as nausea but the presence of depression also complicates symptom management. Hence, poorly controlled N&V lead to physical symptoms and psychosocial distress such as depression, which contributes to a vicious cycle. Returning to the presented case, a young man diagnosed with advanced sarcoma is experiencing chronic N&V, which has negatively impacted his social and vocational functioning. Mirtazapine breaks down the depression-refractory N&V vicious cycle by interacting with multiple neurotransmitter systems and various serotonergic receptor sites, thus improving quality of life.

Due to the compressive effect of the abdominal mass on gastric function and the administration of opioids (Methdone TDD 15 mg) for pain management, leading to delayed gastric emptying, gastroparesis is considered as one of the differential diagnoses in the presented case. Gastroparesis is another cause of chronic and refractory N&V in advanced cancer, which is often underdiagnosed in patients. It is described as an abnormality in gastric motility characterized by delayed gastric emptying without evidence of mechanical outlet obstruction, manifesting as nausea, vomiting, early satiety, and bloating [22]. These symptoms can be disabling, leading to frequent hospitalizations and impaired quality of life. A gastric emptying study was proposed to the patient for diagnostic confirmation; however, the patient declined the procedure. Based on previous studies, medical therapy is typically categorized into two main classes: prokinetics (such as metoclopramide, domperidone, etc.) and symptom modulators (such as ondansetron, promethazine, prochlorperazine, and others) [22]. However, in the case study, neither metoclopramide nor ondansetron relieved the symptoms.

According to several clinical trials, mirtazapine improves gastroparesis symptoms through its agonistic effect on 5HT1A serotonin receptors and antagonistic effect on 5HT2A and 5HT3A serotonin receptors, leading to improved gastric motility and prevention of N&V, respectively [20].

In addition, approximately 23% of idiopathic gastroparesis cases (the most common type) had a history of depression or were receiving antidepressants, which emphasizes that mirtazapine would be a comprehensive medical option in the case [9, 23].

Concerning side effects, somnolence is the most commonly reported with mirtazapine at antiemetic doses (7.5–15 mg). Although tolerance to somnolence develops over time, it remains the most common reason for discontinuation of use [24]. In the presented case, the patient's drowsiness was managed by reducing the dose from 15 to 7.5 mg daily and administering it at bedtime. Despite drowsiness being an adverse effect, in cancer patients who often suffer from insomnia, it may be seen as a positive effect due to mirtazapine's high affinity for H1 receptors, which may improve sleep quality. Other possible side effects include dry mouth, constipation, dizziness, and fatigue [12]. As an antidepressant, mirtazapine has a potential effect on the QT interval [25]. However, previous studies have shown that the maximum therapeutic dose (45 mg) of mirtazapine does not affect the QT interval [26]. Regarding the safety profile of mirtazapine, it is reported to be a safe antidepressant drug in the cancer population. It is almost completely metabolized by the liver and has a low risk of drug interaction, thus allowing its use in advanced renal failure [19].

6 | Conclusion

N&V unrelated to cancer therapy present a challenging symptom management issue in cancer patients. However, in the presented case, based on its pharmacodynamic profile, mirtazapine significantly reduced chronic and refractory N&V in a patient with metastatic pelvic sarcoma who had not responded to standard antiemetic treatments. In addition to improving insomnia, anxiety, and depression, this case highlights mirtazapine's potential to improve quality of life in palliative care settings by providing effective symptom control through a monotherapy

approach, thereby preventing polypharmacy and enhancing patient satisfaction.

Author Contributions

Seyedeh Golnaz Ziaei: data curation, formal analysis, investigation, methodology, software, visualization, writing – original draft. **Mamak Tahmasebi:** conceptualization, project administration, resources, supervision, validation, writing – review and editing.

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Ethics Statement

The study was registered and received ethical approval from the Ethics Committee of Tehran University of Medical Sciences (Code: IR.TUMS.HORCSCT.REC.1403.027).

Consent

Written consent was obtained from the patient to publish this report, following the journal's patient consent policy.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting this study's findings can be obtained by contacting the corresponding author.

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