



PALLIATIVE CARE CASE OF THE MONTH

Reconsidering Mirtazapine: Making the Most of a Side Effect Profile Michelle Freeman, MD

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Case: Mrs. S is a 60 year old woman with a history of breast cancer who is transferred to our hospital from her local institution for evaluation of chronic persistent nausea of unclear etiology that is refractory to treatment. Her issues with nausea began with chemotherapy treatments for breast cancer several months ago. Her breast cancer was treated with partial mastectomy and axillary dissection, followed by neoadjuvant systemic chemotherapy and whole breast radiation, both of which she completed about 3 months ago. Unfortunately, her nausea has persisted, prompting her local physicians to orchestrate an extensive, negative workup of her nausea. She has tried multiple anti-emetics which have been ineffective.

Her persistent nausea impacts her life in many ways. She has lost 5 pounds over the past 3 months since finishing her chemotherapy. For the past two months, she has been feeling depressed and hopeless, which she attributes to her persistent nausea. She also notes increasing anxiety and insomnia. She tried citalopram, but stopped it because of worsening nausea.

Due to her concurrent symptoms of depression, nausea, and insomnia, we started her on mirtazapine 15mg orally at bedtime.

Discussion: Particularly in patients with multiple concomitant symptoms—as is often the case for patients with cancer—it is very important to be economical in our choice of medications for symptom management. It is useful to choose one medication to treat multiple symptoms by utilizing a medication's unique side effect profile.

Mirtazapine (Remeron) is one of a newer class of antidepressants, a noradrenergic and specific serotonergic antidepressant (NaSSA).

It has a unique pharmacologic profile that lends it some useful properties in the treatment of patients with depression and concomitant symptoms of nausea, weight loss, anorexia, and/or insomnia.

Mirtazapine's unique properties make it particularly useful in certain clinical situations and with certain patient populations. Mirtazapine relieves depressive symptoms as well as TCAs, SSRIs, and SNRIs, but takes effect much quicker than SSRIs and SNRIs, making it more effective in the acute-phase treatment of depression (the first six weeks of treatment) compared to SSRIs and SNRIs. Patients often have significant improvement in their depressive symptoms within 2 weeks of starting mirtazapine, sometimes within a few days of starting therapy.

Tolerability of mirtazapine is about the same as tolerability observed for TCAs, SSRIs, and SNRIs, but with a different side effect profile compared to these other medication classes. This makes mirtazapine a useful option when treating depression in patients whose baseline symptoms are exacerbated by SSRIs (as in the case above) or if a patient has intolerable side effects (such as sexual dysfunction) with an SSRI that may be resolved by switching to mirtazapine for antidepressant therapy.

Mirtazapine's side effects can be beneficial to patients with nausea, insomnia and loss of appetite. Mirtazapine's blockade of 5-HT₃ makes it a potentially beneficial option for patients with nausea; this is the same mechanism by which the 'setron (ondansetron, ganisetron, etc.) class of antiemetics and antipsychotics (such as olanzapine) work.

As mirtazapine is dosed once daily, the patient's medication regimen may be simplified if nausea is controlled on mirtazapine, relieving the patient of the need to take an antiemetic multiple times per day. A couple of small studies have suggested that mirtazapine improves appetite and causes weight gain in some cancer patients, making mirtazapine a reasonable option for treatment of depressive symptoms in cancer patients with concomitant nausea, anorexia, and weight loss. Additionally, the sedative effect of low dose mirtazapine can benefit patients with insomnia. Other common side effects of mirtazapine include dry mouth and constipation.

Personal details in the case published have been altered to protect patient privacy.

For palliative care consultations please contact the Palliative Care Program at PUH/MUH, 647-7243, beeper 8511, Shadyside Dept. of Medical Ethics and Palliative Care, beeper 412-647-7243 pager # 8513, Perioperative/ Trauma Pain 647-7243, beeper 7246, UPCI Cancer Pain Service, beeper 644-1724, Interventional Pain 784-4000, Magee Women's Hospital, beeper 412-647-7243 pager #: 8510, VA Palliative Care Program, 688-6178, beeper 296. Hillman Outpatient: 412-692-4724. For ethics consultations at UPMC Presbyterian-Montefiore and Children's page 958-3844. With comments about "Case of the Month" call Dr. Robert Arnold at (412) 692-4834.



(Discussion Continued)

Mirtazapine is usually prescribed with a starting dose of 15mg/day given at bedtime and can be increased as needed every 1-2 weeks; the maximum maintenance dose is 45mg/day. Antihistaminic effects due to potent histamine H1 receptor antagonism are thought to predominate at lower doses, causing drowsiness and sedation; patients should be instructed to take the medication at bedtime. As the dose is increased, noradrenergic neurotransmission increases, which counteracts some of the antihistaminergic effects; thus, the commonly observed side effects of drowsiness and weight gain may be reduced by increasing the dose.

The clearance of mirtazapine is reduced in individuals with hepatic impairment, renal impairment (CrCl < 40 ml/min), and the elderly; in these populations, start with a low dose and increase slowly as needed.

Relevant drug-drug interactions with mirtazapine include medications that can cause serotonin syndrome. Any MAO inhibitor should be stopped more than 2 weeks before initiating mirtazapine and vice versa. There is an increased risk of serotonin syndrome with concomitant use of mirtazapine and medications such as SSRIs, SNRIs, triptans and other serotonergic medications.

Mirtazapine is available as a generic medication and is available in oral tablets (~\$50/month) and oral disintegrating tablets (~\$75/month).

Resolution of the case: Within a few days of beginning mirtazapine, Mrs. S notes significant improvement in her nausea, sleep, and mood. She is very pleased with the early results of treatment and is discharged home with her family.

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