

TAMOXIFEN

Most patients treated with Tamoxifen will experience adverse effects, but the effects will differ from one patient to the next. Symptoms may indicate that the underlying cancer is not under control or has relapses. Cancer patients may also have co-morbid diseases that require treatment and cause symptoms.

The most common adverse effects with Tamoxifen are hot flushes, vaginal discharge, irregular menses, vaginal bleeding, amenorrhea, asthenia/fatigue, mood disturbances, depression, nausea and vomiting, fluid retention- peripheral edema, lymphedema, flushing, skin changes, rash, arthritis/arthritis, and back pain.

ADVERSE DRUG REACTION MANAGEMENT GUIDE

- | | |
|----------------------|---|
| 1. Diarrhea | 9. Osteoporosis |
| 2. Weight loss | 10. Arthralgia, myalgia, bone pain, back pain, musculoskeletal pain |
| 3. Nausea & vomiting | 11. General pain |
| 4. Dyspepsia | 12. Edema |
| 5. Mood disturbance | 13. Hypertension |
| 6. Hair loss | 14. Hot flashes |
| 7. Rash | 15. Flushing |
| 8. Fatigue | |

1. Diarrhea

Diarrhea is common in patients treated with Tamoxifen. Dietary modifications are not recommended in anticipation of diarrhea, but must be considered if diarrhea occurs.

Management:

For mild diarrhea (less than 4 loose stools per day)

- Follow instructions on loperamide (e.g., Imodium®) package insert: 2 tablets immediately, then 1 tablet after each liquid bowel movement (maximum: 8 tablets/24 hours)

For moderate diarrhea (more than 4 to 6 loose stools per day or night-time diarrhea), tell the patient to be more aggressive with loperamide (e.g., Imodium®) for early-onset diarrhea

- Take 2 tablets immediately, then 1 tablet every 2 hours during the day and 2 tablets every 4 hours during the night until bowel movements are normal for at least 12 hours
- This dosage is higher than packaging recommendations.

Replace lost fluids: Fluid intake is more important than eating in patients with diarrhea. To replace lost fluid, advise patients to increase fluids by up to 3 to 4 litres per day (unless there is a known contraindication to increased fluid intake). The patient may drink several types of fluid, including plain water and electrolyte-containing drinks, such as clear broth, gelatin desserts, sports drinks, flat soft drinks, or decaffeinated tea

Anal care: Recommend to your patient to:

- Clean the anal area with mild soap and warm water after each bowel movement to prevent irritation
- Apply a barrier cream or ointment, such as petroleum jelly or Isle's paste
- Soak in a warm bathtub or sitz bath to relieve discomfort

Dietary changes during diarrhea: Advise your patients to change their diet while diarrhea is a problem:

- Eat and drink small quantities of food often
- Avoid spicy, greasy, or fried foods
- Follow the BRAT (banana, rice, applesauce, toast) diet, along with clear liquids, until diarrhea begins to resolve
- Follow a lactose-free diet
- Avoid cabbage, brussel spouts, and broccoli, which may produce stomach gas, bloating and cramps

2. Weight loss

Between 1 and 10% of patients will experience a decreased appetite while taking Tamoxifen.

Prevention: Advise patient to:

- Have several small meals a day
- Eat slowly

Management:

- Light exercise and fresh air may help
- Drink plenty of fluids
- Eat a high calorie meal plan
- Consider Cyproheptadine to stimulate appetite

3. Nausea & vomiting

Nausea and vomiting may occur in up to 25% of patients on Tamoxifen. Unlike the nausea and vomiting often experienced by patients on cytotoxic chemotherapy (acute onset, more emesis than nausea), patients on Tamoxifen tend to have nausea of lesser severity and longer duration, with or without emesis. This can be more distressing to patients' quality of life than acute nausea and vomiting. Often patients will have nausea without the relief that comes from emesis.

Management: The following may provide relief from nausea and vomiting:

- Prophylactic antiemetic agents (e.g. dopaminergic agents such as prochlorperazine, or promotility agents such as metoclopramide) given with each dose of Tamoxifen and repeated as needed for nausea control. While there is no evidence to support the use of dimenhydrinate, there is evidence that ginger products (e.g. Graval[®] Ginger) may be effective, with fewer adverse effects
- Avoid spicy or greasy foods that may contribute to the feeling of nausea. Bland foods, fresh air, and plenty of clear water may reduce the feelings of nausea

4. Dyspepsia

Dyspepsia, or acidic stomach, may be a temporary or chronic problem for some patients. It generally presents as upper abdominal pain, postprandial fullness or early satiety. Dyspepsia occurs in 25% of people, so it may be hard to tell if it is caused by the drug. It may or may not lead to peptic ulcers, but is not usually accompanied by heartburn. Management is often symptomatic and as needed.

Prevention: Advise patients to:

- Avoid foods that cause stomach upset (e.g. spicy foods)
- Avoid lying down after meals
- Reduce alcohol and/or caffeine intake
- Eat smaller meals more frequently
- Reduce stress from daily life

Management:

There are several OTC and prescription treatments to address dyspepsia:

- Antacids (aluminum hydroxide, calcium carbonate, magnesium salts, combinations with or without simethicone for gas)
- Histamine type 2 receptor antagonists (e.g. ranitidine, famotidine)

Proton pump inhibitors (e.g. omeprazole, esomeprazole, pantoprazole, lansoprazole)

5. Mood disturbance

Depression is a mood disorder, which may include features such as diminished interest or pleasure in life, significant gain or loss of weight, sleep disturbances, agitation, fatigue, feelings of worthlessness or guilt, or reduced ability to concentrate. While depression is common in the general population, the incidence is higher in cancer patients. Several drugs can contribute to the severity of depression.

Duration of symptoms may vary between patients.

Management: The following may provide relief from headaches and other general pain problems:

- Psychotherapeutic approaches are often used, including cognitive behavioral therapy and interpersonal therapy. These generally require a referral to a therapist, psychologist or psychiatrist.
- Antidepressant drugs- There are several antidepressant agents in use for this disorder. There are a number of classes of agents used. Pay particular attention to potential drug-drug interactions, to help determine if certain antidepressants should be avoided.

6. Hair loss

About 5% of patients will have hair loss while taking Tamoxifen. Most patients will lose a minimal amount of hair on the oral form of this agent.

Prevention:

- Although there is no way to prevent hair loss, you may advise the patient that hair will usually regrow, once the treatments are over. The replacement hair may have a different colour or consistency.

Management:

If hair loss bothers the patient, a wig, hat, cap, scarf or hair piece may be worn

7. Rash

Rash is a common adverse effect of Tamoxifen. Rash symptoms often appear soon after starting treatment. This rash presents with spots and bumps on the forearms, trunk, and sometimes, the face. They are often itchy, but if scratched, may become infected and crusty. Most cases of this generalized skin rash are mild and go away on their own. Rash is more common in women and patients on higher doses, and may worsen after sun exposure.

It is important to recognize rash symptoms early and start symptomatic therapy promptly.

Prevention: Prevention should begin when Tamoxifen therapy is begun, and continue throughout treatment.

You should advise your patient to:

- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness
- Moisturize twice a day with thick, emollient-based creams, such as Aveeno® lotion, Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion
- Use only fragrance-, alcohol-, and dye-free lotions and cosmetics
- Use a dermatologist-approved cover-up, such as Dermablend® or Cover FX®
- Remove make-up with a gentle, skin-friendly cleanser (e.g., Neutrogena®, Dove®).
- Use a broad-spectrum sunscreen (SPF of 30 or more) that contains zinc oxide or titanium dioxide

Management: For Mild to moderate skin rash, there are some over-the-counter options you may consider:

- Antihistamine (diphenhydramine)
- Topical steroid (hydrocortisone 0.5%)
- Coal tar preparations

If the rash progresses to moderate to severe, the patient may need prescribed therapy:

- Oral corticosteroids (short course, with or without topical triamcinolone acetonide 0.1% ointment)
- Temporary interruption of therapy until the rash resolves, and then re-challenge at low dose

8. Fatigue

About 20% of patients on Letrozole will experience fatigue. This symptom is not life-threatening but will significantly reduce quality of life.

Management: The following may provide relief from fatigue:

- There are no medications that have demonstrated an effect to relieve fatigue
- Mild exercise is very helpful to reduce fatigue, but must be manageable if there is also muscle weakness

9. Osteoporosis

Osteoporosis is the loss of bone mineral density, resulting in skeletal fragility. It affects 1 in 4 women and 1 in 8 men, increasing in older adults. The more the bones thin out, the greater the risk of fracture. Osteoporosis may be increased with some medications.

Prevention:

- Take 1000 mg calcium and at least 400U (10 mcg) Vitamin D supplement daily. This is available OTC.
- Add weight-bearing exercise (e.g. walking, jogging) to daily activities.

Management:

- Prescription bisphosphonate therapy (e.g. alendronate, etidronate, risedronate) may be added to calcium and vitamin D.

10. Arthralgia, myalgia, bone pain, back pain, musculoskeletal pain

Aching bones or muscles and muscle cramps occur in 5-10% of patients taking Tamoxifen. Muscle cramps may occur in the hands, feet, calves, or thighs. Cramps have been described as sustained muscular contractions that follow a consistent pattern, frequency, and severity. Muscle cramps may be related to exertion or could happen at night. Patients should avoid using quinine or drinking tonic water (contains quinine).

Bone and joint pain may begin in the first month of therapy and commonly subside after a few months. Pain may affect the leg bones, hips, and knees, and may appear in an asymmetrical pattern. Although there are no evidence-based guidelines for prevention or treatment, anecdotal reports and expert experience suggest that some patients' pain could be eased by using mineral supplements.

Management: The following may provide relief from muscle aches or cramps:

- Calcium and magnesium supplements
- Mild pain medications- Acetaminophen preferred; do NOT use non-steroidal anti-inflammatory agents, prescription or OTC due to risk of bleeding (e.g. ibuprofen, ASA, naproxen)
- For bone or joint pain, consider the use of heating pads, ice packs, or topical arthritis creams and liniments
- Mild exercise and/or massage therapy may help reduce bone and joint pain
- Avoid using quinine or drinking tonic water.

11. General pain

Patients on Tamoxifen may experience other types of pain. About 8-10% of patients have headaches while on this treatment. Generalized pain maybe a drug side effect or may be related to the cancer.

Management: The following may provide relief from headaches and other general pain problems:

- Mild pain may respond to non-pharmacologic approaches, such as rest, distraction, cool cloth on the forehead
- Mild pain medications- Acetaminophen preferred; do NOT use non-steroidal anti-inflammatory agents, prescription or OTC due to risk of bleeding (e.g. ibuprofen, ASA, naproxen)

- Acetaminophen with codeine, either OTC (low dose) or on prescription (higher dose) may be considered for more severe pain.
- If acetaminophen is not sufficient to control pain, consider prescription opioid analgesics for management of more severe pain (possibly due to tumor)
- If there is a neuropathic component to the pain, consider a trial with a tricyclic antidepressant (e.g. low dose amitriptyline or imipramine) or gabapentin

12. Edema

Fluid retention (edema) is a common side effect in patients taking Tamoxifen. Peripheral fluid retention is usually superficial and mild to moderate in severity. The most common form of edema is swollen eyelids or swelling around the eyes (periorbital edema), which is worse in the morning and often associated with swelling of ankles, feet, and lower legs. This type of fluid retention tends to get better over time, occurring more frequently in women, adults older than 65, and patients with a history of heart or kidney problems.

Pleural effusion (excess fluid around the lungs) may occur in patients taking Tamoxifen. It is more common on patients being treated with higher doses of Tamoxifen, or with a history of heart disease, hypertension, rash, autoimmune disease, and high cholesterol. Pleural effusion may occur anytime from 5 weeks to 1 year after the start of treatment. Patients should be monitored for early signs of fluid retention: dry cough, shortness of breath, and tight chest.

Early intervention is critical; refer patient to a doctor for immediate care. Advise patients to weigh themselves regularly and report any weight gain greater than or equal to 5 lbs. Central fluid retention in or around the lungs, stomach, central body tissues, heart, or brain (often associated with rapid weight gain) is potentially life-threatening.

Prevention:

- Limit salt intake.
- To prevent swollen eyelids or swelling around eyes, elevate head while sleeping.

Management:

- For mild swelling around eyes, elevate head during sleep or use skin-tightening agents (e.g. topical Preparation H®) containing phenylephrine or lanolin (avoid eye contact). This is available OTC.
- For mild periorbital fluid retention, topical eye ointments with phenylephrine 0.25% or topical corticosteroids (e.g. hydrocortisone 1%)
- For moderate fluid retention, consider a low-dose loop diuretic (e.g. furosemide with calcium and magnesium supplements) and close electrolyte monitoring

13. Hypertension

Patients on Tamoxifen should be monitored for the onset or worsening of hypertension. If you have a blood pressure monitoring device, consider checking the patient's blood pressure when they visit the pharmacy and report any elevation to the cancer care team. Hypertension is usually mild to moderate

and manageable with standard antihypertensive therapy. Management may be done by either the cancer care team of the family physician- *BUT beware of any potential drug interactions as new antihypertensive therapy is initiated.*

14. Hot flashes

Hot flashes (or hot flushes) can be very troublesome for many patients. Waves of heat sensation may occur without warning, similar to the hot flashes from female menopause.

Prevention: Advise the patient to:

- Keep room temperature lower, if possible
- Dress in layers, so layers can be removed if hot flushes become uncomfortable
- Natural health products may be tried, such as black cohosh, phytoestrogen supplements, evening primrose oil, dong quai, or ginseng. Evidence of benefit is lacking for most of these products. Watch for potential drug-drug interactions with the herbal product before advising use.
- Accupuncture has been tried for relief of hot flushes, but there is no evidence of effectiveness
- Psychoeducational interventions, as sometimes offered by psychosocial support teams in the cancer centres, may help patients to find ways to improve these symptoms

Management:

- Try systemic treatment with clonidine, venlafaxine, paroxetine or gabapentin (prescription); evidence of benefit is minimal, and drug side effects may limit use for some patients.

15. Flushing

Flushing is a reddening of the skin, often accompanied by a feeling of heat. It is caused by local vasodilation. Flushing can be very troublesome for many patients.

Prevention: Advise the patient to:

- Keep room temperature lower, if possible
- Dress in layers, so layers can be removed if hot flushes become uncomfortable
- Psychoeducational interventions, as sometimes offered by psychosocial support teams in the cancer centres, may help patients to find ways to improve these symptoms

REFERENCES:

ONTarget Resource Guide, Common Side Effects from Targeted Therapy. The Groupe d'étude en oncologie and The Canadian Association of Pharmacy in Oncology, 2012.

Systemic Therapy Manual for Cancer Treatment, Cancer Care Nova Scotia, 2013

Patient Self-Care. Helping Your Patients Make Therapeutic Choices. Canadian Pharmaceutical Association , 2010

Therapeutic Choices, Sixth Edition, Canadian Pharmaceutical Association , 2011