Oral Systemic Therapy- Adverse Drug Reaction Management Guide

LAPATINIB

Most patients treated with Lapatinib 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 Lapatinib are diarrhea, nausea, and vomiting, rash, and fatigue.

ADVERSE DRUG REACTION MANAGEMENT GUIDE

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1. Myelosuppression

Lapatinib may cause suppression of the blood cell production in the myeloid tissues of the bone marrow. This can result in lowering of white blood cells and platelets. It is important to have a Complete Blood Count (CBC) blood test prior to the start of each cycle of this agent. If any blood cell component is reduced below an acceptable level, the drug may need to be held until the blood cells recover. **Lapatinib must NOT be dispensed** until the CBC test is completed and verified prior to each cycle of the treatment. Verification will be done by an oncology health professional.

Prevention: General infection preventative measures should be followed while on this drug, especially if the blood counts are low. Advise patient to:

- Limit contact with people who are sick, have colds, or have been recently vaccinated
- Rest often
- Do not eat uncooked vegetables
- Wash hands often

If the platelet count is low, tell the patient to take. Advise patient to:

- Take care when shaving or performing any activity of daily living where the skin could be cut
- Use a soft toothbrush.
- Tell your doctor before dental work is done.

Counseling tips:

Reinforcement is important. Make a note to yourself (or book a time for a follow up call) to repeat these suggestions 2-3 weeks after the Lapatinib treatment initiation or any report of early rash symptoms.

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Management: If the patient has a fever or other signs of an infection when the blood counts are low, advise him/her to go directly to the Emergency Department and contact the oncologist when there. The ER staff needs to be told that the patient is taking this drug, and that it is a form of chemotherapy. Empiric antibiotics will be required.

If the patient has unusual bleeding when the platelet counts are low, advise him/her to go to the Emergency Department, tell the ER staff about this drug, and contact the oncologist when there.

2. <u>Rash</u>

Rash is a common adverse effect of Lapatinib, occurring in up to 43% of patients. Early preventive strategies may help to reduce severity of skin rashes. Most Lapatinib-related rashes are mild to moderate in severity and inflammatory rather than infectious. Rash usually develops early in treatment. Rashes usually appear on the trunk and infrequently on the face. Pruritis is rare. The rash usually resolves during treatment, after a temporary interruption in treatment, or when therapy ends. To determine how best to manage the rash, you should ask patients about other symptoms they may be experiencing. These symptoms may signify a need to refer patients to a doctor or dermatologist. These symptoms include:

- Burning
- Edema
- Itchiness
- Redness
- Tender skin

Prevention: Being proactive is critical in managing rash.

When your patient begins therapy, you should advise him/her to:

- Cleanse with mild soaps or hypoallergenic cleaners or bath or shower oils to avoid skin dryness
- Take short showers with warm water
- 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 skin rash (localized, reddish skin spots or bumps without other symptoms, no impact on daily activities, no sign of infection), there are some options you may consider:

- Topical steroid (hydrocortisone 0.5%)
- Topical agents with anti-inflammatory properties (hydrocortisone 1%-2.5% cream, metronidazole cream, or clindamycin 1% cream or topical solution)

Advise the patient to monitor the rash for changes in severity. If the rash persists after 2 weeks of treatment or worsens in severity, refer to doctor.

If the rash progresses to moderate (localized skin peeling or sloughing; reddish skin spots or bump with other symptoms such as redness, itchiness, burning, swelling, or tenderness; lesions cover < 50% of body surface; minimal impact on daily activities), the patient may need prescribed therapy:

- Hydrocortisone 2.5% cream, clindamycin 1% cream or topical solution, or pimecrolimus 1% cream

PLUS

- Doxycycline (100 mg BID PO) or minocycline (100 mg BID PO)

Advise patient to monitor the rash for changes in severity and to consult doctor if symptoms persist or worsen after 2 weeks of treatment.

Counseling tips:
Tell your patient about prevention of HFSR early in the treatment. If the patient is not prepared for detailed counselling on the day the prescription is picked up, plan a follow up call in a couple of days.

3. <u>Hand-foot skin reactions (when given with Capecitabine)</u>

Hand-foot skin reaction (HFSR), also known as hand-foot syndrome and palmar-plantar erythrodysesthesia, is an uncommon side effect of Lapatinib. HFSR is a potentially dose-limiting, skin-related side effect if not managed and prevented at an early stage.

If the patient tells you on the call back phone call he/she is bothered by pain in the hands or feet, you might want to **have the patient drop by the pharmacy** for you to have a look and determine if any prevention or management is required.

Prevention: Prevention of traumatic activity and rest are crucial.
Urge your patients to:

- Have a manicure or pedicure to remove thickened skin or calluses; follow with moisturizing cream
- Use a moisturizing cream (e.g. Udderly Smooth®, Bag Balm®)
- Wear loose-fitting, soft shoes or slippers, foam absorbing soles, gel inserts to cushion pressure points, cotton socks
- Cushion callused areas with soft or padded shoes
- Reduce exposure of hands and feet to hot water (showers, dishwashing, etc.)
- Avoid excessive friction to hands or feet when performing tasks
- Avoid vigorous exercise or activities that place undue stress on the hands and feet
- Wear thick cotton gloves or socks to protect hands and feet and keep them dry
- Report any signs or symptoms immediately to ensure early-stage treatment

Management: For *Mild* HFSR, there are several management strategies you may consider:

- Avoid hot water; cool water or cold compresses may ease symptoms
- Diligently apply moisturizers to keep palms and soles soft and pliable to prevent cracks or breaks in skin integrity- Use moisturizing creams twice daily; also use aloe vera lotion as needed and use 20% to 40% urea cream or 6% salicylic acid on callused areas
- Soak feet in magnesium sulfate (Epsom salts) to soften calluses and reduce pressure pain

- Use low to moderate dose pain killers
- Advise patients to consult their doctor about reducing their dosage of Lapatinib, if symptoms of HFSR worsen after being treated for 2 weeks

For *Moderate to Severe* HFSR, the patient will likely need prescribed therapy, such as:

- Topical corticosteroid (e.g., clobetasol 0.05% ointment)
- 2% lidocaine topical ointment
- For thick, tender sores after acute rash with/without blisters resolves: 40% urea cream; or Tazarotene 0.1% cream; or Fluorouracil 5% cream
- Dose modification of the Lapatinib

4. Xerosis (dry skin)

Xerosis (dry skin) occurs in as many as 10% of patients treated with Lapatinib. Dry, scaly, itchy skin resembling atopic eczema usually begins anywhere from 1 week to 3 months after starting therapy; it is persistent and often lasts several months. This dry, scaly skin may appear on the limbs, torso, and areas of EGFR-induced rash. It often affects the fingertips, heels, and toes. Painful fissures may develop in these areas, in nail folds, and over finger joints in excessively dry skin. This can make wearing shoes or performing tasks difficult. Dry skin may become increasingly fragile and bruise easily. Xerosis may worsen, becoming chronically red and irritable. Secondary infection with *S. aureus* may occur. General measures to hydrate the skin and choosing the right treatment is critical to alleviating skin dryness. Frequent application of emollients that contain ammonium lactate (e.g., hydrolac or Lac-Hydrin®) or 5% to 10% urea (e.g. Eucerin® 5 or Uremol® 10) may significantly improve dryness. Instruct the patient to avoid occlusive topical creams and lotions, as they may obstruct hair follicles and thus lead to infection.

Prevention: Advise patients to:

- Cleanse with mild soaps or cleaners or bath or shower oils to avoid skin dryness
- Take short showers with warm water
- Moisturize twice a day with a colloidal oatmeal lotion, such as Aveeno® lotion, or thick, emollient-based creams, such as Neutrogena® Norwegian Formula hand cream, or Vaseline Intensive Care® Advanced Healing Lotion
- Use only fragrance- , alcohol-, and dye-free lotions and cosmetics
- Remove make-up with a gentle, skin-friendly cleanser, e.g., Neutrogena®, Dove®

Management:

- At the first signs of skin dryness; dry skin on face, back, and chest: advise patient to switch to oil-in-water creams.
- For moderate to severe xerosis; dry skin on limbs: Use greasy water-in-oil creams or ointments.
- For eczema, recommend short-term use (1-2 weeks) of weak topical corticosteroid creams. Refer to doctor if it is not controlled by OTC treatment.

- For infection, recommend topical antibiotics. Refer to doctor if it is not controlled by OTC treatment.
- For skin fissures, treatment options include:
    - 50% propylene glycol under a plastic bandage
    - Salicylic acid 10% ointment
    - Colloid dressing

  Refer to doctor if it is not controlled by OTC treatment.

5. Paronychia

Paronychia is a painful inflammation that occurs around finger and toenails in up to 19% of patients. It usually appears within 4-8 weeks or up to 6 months after therapy begins. While this is not infective in origin, paronychia makes nails more sensitive to infection. Nails tend to grow slower, become brittle, and crack. Paronychia can be painful and mimic an ingrown nail. It may interfere with simple manual work or prevent the patient from wearing any shoes but sandals. It can take weeks to heal and may not resolve unless therapy stops for a short period or ends. In severe cases, abscesses and small, red, oozing, and bleeding bumps that look like raw hamburger meat develop in nail folds. (**Refer to a dermatologist or a family physician; a podiatrist cannot provide adequate foot care in this situation.**)

Prevention: Advise your patients to:

- Wear comfortable, loose-fitting shoes to avoid friction or pressure on nail folds
- Avoid biting nails or cutting them too short

Management:

OTC treatment:

- Topical antiseptics or antibiotics (soaks or creams) to prevent or treat mild infection
- Epsom salts or Buro sol® (aluminum acetate) soaks daily
- Weekly application of topical silver nitrate to treat hamburger-like bumps
- Foot cushioning products for extra comfort.

Prescription medication:

- Topical antimicrobials, such as mupirocin and nystatin ointment
- Topical corticosteroid, such as 1% triamcinolone ointment
- Doxycycline, 6-week course of 100 mg twice daily

Refer to doctor for pain in nail bed, nail loss, signs of infection.

6. Stomatitis

Stomatitis (mouth sores) is a common side effect of Lapatinib (14% of patients will develop stomatitis). Integrity of mucous membranes may be affected by Lapatinib treatment, leading to the swelling and reddening of membranes lining the mouth. Mouth sores or cankers may develop. Patients may complain of changes on the inner cheeks or mouth surfaces, even when mouth sores are not present or only a mild redness is evident. Patients may experience:

- Mouth pain

- Difficulty chewing
- Painful swallowing (dysphagia)

This side effect may lead to SUNItinib dosage reductions. It is important to maintain good oral health during treatment. Aggressive prevention may reduce incidence and severity of stomatitis. Treatment during stomatitis event(s) can relieve symptoms (including oral pain, oral bleeding, dental complications, soft tissue infection and dietary restrictions) and restore oral health, often within 7 to 14 days.

Prevention and Management: Good oral care is the key to prevention of stomatitis. If possible, the patient should work with their dentist (and oncologist) to correct any pre-existing dental problems before starting Lapatinib treatment. Careful and thorough oral hygiene is important, and particularly irritating foods (e.g. very spicy foods, rough textures, alcohol-containing foods or liquids) should be avoided.

Management may be achieved in many patients without prescribed therapies. Most important is meticulous oral hygiene:

- Toothbrushing, 3-4 times daily with soft-bristle toothbrush. Soak toothbrush in warm water to soften bristles
- If brushing is painful, Toothettes (sponge-tipped stick with toothpaste), sponges, or gentle use of Waterpik®
- Biotene toothpaste is non-irritating contains natural salivary enzymes to control bacteria
- Floss gently once daily to avoid gum injury
- Salt and baking-soda rinses (1/2 teaspoon of each ingredient in 1 cup of warm water at least 4 times daily, especially after meals)
- Bland rinses, antimicrobial mouthwash (non-alcohoic)
- OTC analgesics, such as ibuprofen (e.g., Advil®, Motrin®) and acetaminophen (e.g., Tylenol®).

If the patient has difficulty eating or drinking sufficient fluids or if redness is associated with lesions on the inner cheeks, tongue or lips, contact the cancer care team at once and tell the patient to contact the oncology nurse or oncologist for immediate advice or a visit.

Topical preparations in widespread use for chemotherapy-induced stomatitis contain ingredients such as lidocaine, benzocaine, milk of magnesia, kaolin, pectin, and diphenhydramine. Although there is no significant evidence of the effectiveness or tolerability of these combinations, there may be a degree of symptom management (e.g. oral pain, improved ability to maintain a proper diet). Salt-and-baking soda rinses may help. Chlorohexidine mouth rinses are not recommended, as they contain alcohol and may sting. Hydrogen peroxide may worsen mouth ulcers. In addition, mouthwash preparations containing *antifungals* (i.e. nystatin), broad-spectrum *antibiotics*, or *corticosteroids* have shown no benefit and possibly further worsening of stomatitis- ***these combinations are not recommended!***

7. Nausea & vomiting

Nausea and vomiting may occur in up to 45% of patients on Lapatinib. Unlike the nausea and vomiting often experienced by patients on cytotoxic chemotherapy (acute onset, more emesis than nausea), patients on Lapatinib 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 Lapatinib 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. Gravol® 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

8. Diarrhea

Diarrhea is very common in patients treated with Lapatinib; 65% of patients experience diarrhea. Dietary modifications are not recommended in anticipation of diarrhea, but must be considered if diarrhea occurs.

Management:

When patients seek OTC treatment for diarrhea, it is important to ask them about:

- Number of stools per day and stool composition, e.g. watery, presence of blood, nocturnal
- Presence of diarrhea before their last treatment
- Medication profile to identify other agents that may contribute to diarrhea
- Dietary profile
- Signs and symptoms of complicated diarrhea, including
    - Blood in stool
    - Dehydration, e.g. oral dryness, low urine production or dark yellow urine, weight loss, dry eyes or mouth, sunken eyes, low pulse, dizziness or feeling faint when getting up
    - Fever
    - Lethargy or altered mental state
    - Nausea and vomiting
    - Signs of infection
    - Stomach cramps

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

When to refer: 14% of patients will develop severe diarrhea. Urge these patients to consult their doctor for treatment if:

- They do not respond to loperamide after >24 hours
- Fever is present

9. Constipation

Constipation is generally understood to be a reduction in bowel movements to fewer than 3 per week, or unsatisfactory (e.g. incomplete) defecation. Reduced bowel function may give the misperception of constipation to patients who expect one or more movements daily. Constipation may be caused by this medication, other medications being taken concurrently (e.g. narcotic analgesics), or by the underlying cancer. Reduced physical activity or dietary changes, possibly related to this medication or the overall cancer treatment, may contribute to constipation. Abdominal pain is often associated with constipation, but if symptoms become severe a medical assessment to examine for fecal impaction or bowel obstruction may be needed.

Prevention: Advise patient to:

- Change diet, if possible, to include more fruits, vegetables, and high-fibre foods. If the patient is taking a low-calorie diet, consider increasing calories to improve colonic transit.
- Use of a regular laxative regimen, such as senna or bisacodyl at bedtime
- Consider a bowel routine to maintain regularity, such as attempting bowel movements each morning after breakfast (usually the optimal time for a movement), using the toilet when there is an urge instead of repressing it, placing a footstool in front of the toilet to elevate thighs during movement.
- Consider adding light exercise for patients with mostly sedentary lifestyles
- Weight loss in over-weight patients may help improve bowel function

Management:

- If prophylactive stimulant laxative is not effective, try osmotic laxative (e.g. lactulose or PEG)
- Stool softeners have not been shown to be effective
- Drink of fluids
- Biofeedback and relaxation techniques may help some patients with pelvic floor dysfunction. Psychosocial teams in the cancer centres may help with this type of intervention.

10. Anorexia

Up to 15% of patients will experience a decreased appetite while taking Lapatinib.

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

11. 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. ranitindine, famotidine)
- Proton pump inhibitors (e.g. omeprazole, esomeprazole, pantoprazole, lansoprazole)

12. Fatigue

About one quarter of patients on Lapatinib 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

13. Insomnia

Insomnia, or the inability to fall asleep and/or stay asleep, may be a symptom of depression, a drug side effect, a reaction to unresolved pain, or a natural reaction to daily stress and worries (e.g. about the cancer). Many drugs can contribute to insomnia problems.

Prevention: Advise patients to:

- Avoid alcohol, nicotine (e.g. smoking, nicotine supplements) and caffeine intake, especially in the evening
- Avoid large meals late in the evening
- Use earplugs and/or eye masks if helpful. Turn the clock face away from sight and use the alarm daily.
- Try relaxation exercises
- Maintain a regular pattern of timing for going to bed and rising, 7 days a week. Limit mid-day naps. Do not sleep in on weekends or free days.
- Regular aerobic exercise (e.g. walking) during the day can help stimulate the need for sleep at night. Exercise should be enough to cause sweating, with a duration of 30 to 40 minutes daily. Do not overexert if there are other physical limitations to exercise

Management: There are many medications (prescription and OTC) used for insomnia. Try to start with the least potent options and limit use to short periods if possible.

- Common OTC products contain diphenhydramine or doxylamine. These products may help patients to fall asleep.
- Natural health products have limited evidence of effectiveness, but are often used. Products may contain Valerian or Melatonin.

- Prescription hypnosedatives may be considered. Options include benzodiazepines (e.g. lorazepan, flurazepam) and non-benzodiazepines (e.g. zopiclone).

14. Back pain

Back pain can occur in about 10% of patients taking Lapatinib.

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

- 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 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 joint pain
    - Use of a muscle relaxant may be considered (e.g. cyclobenzaprine- prescription, or acetaminophen/methocarbamol combinations-OTC)

15. Arthralgia

Aching joints or arthritic pain is a common co-morbidity in cancer patients and can be initiated or exacerbated by some medications.

Prevention:

- Some light exercise (e.g. walking, jogging) and regular physical activity will help reduce pain and discomfort, even if it is painful to start some activities.

Management:

- Acetaminophen on a regular basis may help to manage pain. Try the controlled-release product, 1 or 2 tablets every 8 hours. Be careful not to take too much Acetaminophen (i.e. limit Acetaminophem from other sources, such as PRN dosing or Acetaminophen-containing narcotic analgesics
- Do NOT use systemic non-steroidal anti-inflammatory agents, prescription or OTC due to risk of bleeding (e.g. ibuprofen, ASA, naproxen)
- For 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 joint pain
- If the arthralgia persists, see a physician, and tell them about all medications, including the cancer treatment drugs

16. Myalgia

Aching muscles and muscle cramps cqn be very disruptive, lowering patient quality of life. 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).

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

- 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)
- Use of a muscle relaxant may be considered (e.g. cyclobenzaprine- prescription, or acetaminophen/methocarbamol combinations-OTC)

17. General pain (headache)

Patients on Lapatinib may experience other types of pain. About 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

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