THE USE OF DEXAMETHASONE IN PATIENTS WITH HIGH GRADE GLIOMAS

Effective Date: March, 2013

The recommendations contained in this guideline are a consensus of the Alberta Provincial CNS Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

Patients with primary brain tumours often develop vasogenic edema and increased intracranial pressure. Corticosteroid therapy improves this in three quarters of patients, generally within 48 hours.¹ As such, corticosteroid therapy is a necessary pre-requisite to embarking on radiotherapy following surgery, particularly in patients whose brain tumours exert a significant mass effect. Similarly, management of edema and intracranial pressure with corticosteroids forms an integral aspect of treatment in the post-radiotherapy phases of care. Dexamethasone is the usual corticosteroid of choice, because of its minimal mineralocorticoid activity, long half-life, and high potency. Despite its common use, however, there have been few prospective clinical trials to determine the optimal dose and schedule for dexamethasone in patients with primary brain tumours, and subsequently fewer clinical practice guideline recommendations. Dexamethasone and all steroids are associated with a variety of side effects, therefore the risks and benefits must be weighed carefully for each patient. The goals of this guideline are to review the evidence for the use of dexamethasone in patients with high-grade gliomas, to describe the management of side effects associated with dexamethasone use in this patient population, and to document the recommendations of the Alberta Provincial CNS Tumour Team for the use of dexamethasone in patients with high-grade gliomas.

GUIDEINE QUESTIONS

• When should dexamethasone be considered in adult patients with high-grade gliomas?
• What are the optimal dose ranges?
• What is the optimal schedule for dexamethasone tapering?
• What are the most common adverse events associated with dexamethasone therapy, and how are they best managed?

DEVELOPMENT AND REVISION HISTORY

Evidence was selected and reviewed by a working group comprised of a medical oncologist, a pharmacist, and a knowledge management specialist, with input from an endocrinologist. The working group drafted the recommendations and guideline, and distributed this document for review and comment to members of the Alberta Provincial CNS Tumour Team (N=30) via an anonymous electronic survey. The response rate was 33%. The final guideline was reviewed and endorsed in February 2013 by the Alberta Provincial CNS Tumour Team. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

SEARCH STRATEGY

Medical journal articles were searched using the Medline (1948 to Nov Week 3 2012), PubMed (1950-Nov 2012), Cochrane Database of Systematic Reviews (2005 to Nov 2012), and CINAHL (1982 to Nov 2012) electronic databases. Search terms included dexamethasone OR glucocorticoids OR corticosteroids OR decadron OR adrenal cortex hormones AND brain tumour or glioma OR high-grade glioma OR brain neoplasm. The reference lists of relevant articles were hand searched for additional articles. In addition to the Guideline Clearinghouse database, the websites of the following guideline developers were searched for relevant content: the American College of Radiology (ACR), the Australian Cancer Network, the British Columbia Cancer Agency (BCCA), Cancer Care Ontario (CCO), the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the National Institute for Health and Clinical Excellence (NICE). A search of the grey literature was also conducted using Google and Google Scholar. The patient population was limited to adolescents and adults; there were no
limitations by date, publication type, or study design. The literature search resulted in eight publications which were used to formulate the final recommendations addressing the first three guideline questions. To address the fourth guideline question, a systematic review of the literature was carried out incorporating the MeSH terms listed above in combination with the following keywords: hyperglycemia, myopathy, osteoporosis, avascular necrosis, peptic ulceration, bowel perforation, anxiety, irritability, insomnia, mania, psychosis, depression, seizures, infections, Pneumocystic jirovecii pneumonia, candidiasis, venous thromboembolism, hypertension, cardiovascular complications, weight gain, Cushingoid, hirsutism, fragile skin, and skin complications.

TARGET POPULATION

Adult patients with primary high-grade gliomas.

RECOMMENDATIONS

1. Treatment with dexamethasone is recommended for symptom relief in patients with primary high-grade gliomas and cerebral edema.
2. Following surgery, a maximum dose of 16 mg daily, administered in four equal daily doses is recommended for symptomatic patients; this protocol should ideally be started by the neurosurgeon.
3. Dexamethasone should be tapered in a manner individualized to each patient; we recommend one of three taper schedules:
   a. Slow Taper: starting with 4 mg twice daily for 7 days, then 2 mg twice daily for 7 days, then 1 mg twice daily for 7 days, then 1 mg once daily for 7 days
   b. Fast Taper: dexamethasone can be discontinued within 3 days of surgery
   c. Individualized Taper: a taper schedule individualized for a specific patient as decided upon by the physician.
4. Patients who have high-grade tumours, are symptomatic, or have a poor life expectancy, can be maintained on a 0.5-1.0 mg daily dose of dexamethasone.
5. Side effects of dexamethasone are common, and increase in frequency and severity with increased dose and duration of therapy. Patients should be carefully monitored for endocrine, muscular, skeletal, gastrointestinal, psychiatric, and hematologic complications, as well as for infections and other general side effects.

DISCUSSION

Patient Selection

The Alberta Provincial CNS Tumour Team recommends treatment with dexamethasone for symptom relief in patients with primary high-grade gliomas and cerebral edema.

Dosing

Table 1 summarizes the dosing recommendations from published clinical practice guidelines addressing the use of dexamethasone in patients with primary brain tumours. These recommendations are all based on lower levels of evidence such as case series and retrospective reviews.
Table 1. Recommendations for dexamethasone dosing from published clinical practice guidelines.

<table>
<thead>
<tr>
<th>Guideline Developer</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCN, 2013</td>
<td>• In general the lowest dose of steroids should be used for the shortest time possible.</td>
</tr>
<tr>
<td></td>
<td>• Downward titration of the dose should be attempted whenever possible.</td>
</tr>
<tr>
<td>Australian Cancer Network, 2009</td>
<td>• The usual starting dose is 16mg per day.</td>
</tr>
<tr>
<td></td>
<td>• The dose of dexamethasone should be gradually tapered to the lowest amount that controls the patient’s symptoms; dexamethasone should not be discontinued abruptly.</td>
</tr>
<tr>
<td>BC Cancer Agency, 2004</td>
<td>• Dexamethasone is used most commonly in a range of doses from 2-16 mg per day (in divided doses) depending on symptom severity. In emergent situations, higher doses of dexamethasone may be used and mannitol may also be employed.</td>
</tr>
<tr>
<td></td>
<td>• During radiation therapy, a tapering dose of dexamethasone, as clinically tolerated (to alleviate symptoms of brain edema), is prescribed, and the lowest effective dose is used. After completion of radiation therapy, the dexamethasone is tapered and discontinued over 2 - 4 weeks usually.</td>
</tr>
<tr>
<td>American College of Radiology, 1999</td>
<td>• For patients with minimal neurological symptoms, the committee recommends either starting with 4-8 mg/day of dexamethasone or starting with 16 mg/day of dexamethasone but tapering after a few days.</td>
</tr>
<tr>
<td></td>
<td>• In all cases, steroids should be tapered as clinically indicated and tolerated.</td>
</tr>
</tbody>
</table>

The literature addressing the use of dexamethasone for adult patients is limited and conflicting, and primarily describes patients with brain metastases. In a review describing the prescribing practices of oncologists and palliative care specialists for their patients with brain metastases, Sturdza and colleagues reported that 45 percent of surveyed physicians routinely prescribed dexamethasone at a fixed dose of 16 mg daily for all patients with brain metastases. The presence or absence of symptoms, types of symptoms, types of neurological deficits, and degree of edema on imaging were all factors cited by the physicians who chose to prescribe a dose other than 16 mg daily.

In a systematic review of 21 randomized controlled trials of whole brain radiotherapy (WBRT) for patients with multiple brain metastases, Millar and colleagues reported that, of the 18 studies documenting steroid use, only five provided details on the type and dose of steroid. Dexamethasone was the most commonly used steroid, and doses ranged from 8 to 16 mg/day in four studies, while one study reported the use of prednisone at 40 mg daily. In a study reporting the results of two consecutive randomized trials involving 96 patients with brain metastases, Vecht et al. compared 4, 8, and 16 mg daily dosing of oral dexamethasone. They reported more toxic effects in the patients treated with 16 mg daily and no significant improvements in Karnofsky performance scores (KPS) when compared to the lower doses. The authors concluded that for the majority of patients, lower doses of 4 or 8 mg daily have an equivalent effect on neurologic performance.

The majority of retrospective studies and reviews report the most common starting dose of dexamethasone to be between 8 and 16 mg per day. In a recent review of the role of steroids in the management of brain metastases, Ryken and colleagues concluded that symptomatic patients should be treated with a starting dose of 4 to 8 mg daily; if the patient exhibits severe symptoms associated with increased intracranial pressure, a dose of 16 mg/day or higher could be considered. Two recent comprehensive reviews recommend an initial loading dose of 10 to 20 mg of intravenous dexamethasone when the patient presents with acute neurological symptoms caused by a brain tumour or spinal cord lesion; this should be followed by maintenance dosing with oral or intravenous dexamethasone at a daily dosage of 4 to 24 mg in divided doses.
Based on the literature published to date, the Alberta Provincial CNS Tumour Team members recommend a **maximum** starting dose of 16 mg daily, administered in four equal daily doses, for symptomatic patients following biopsy or surgical resection.

**Dexamethasone Tapering**

Most patients begin to improve symptomatically within hours of dexamethasone administration, and achieve a maximum benefit within 24 to 72 hours. There is a high-rate of side-effects associated with prolonged dexamethasone use, as well as a risk of suppression of the hypothalamic-pituitary-adrenocortical (HPA) axis; therefore, dexamethasone should be tapered once symptoms begin to improve. The published evidence and recommendations regarding the optimal tapering schedule are varied. In general, the most commonly reported tapering schedules involve a gradual decrease in the dose or dosing interval over a period of two to four weeks to prevent rebound symptoms, with a longer period for symptomatic patients. Some publications favour tapering until a physiologic dose equivalent to 20 mg per day of cortisol is achieved, which might be 0.25 mg dexamethasone daily. Other publications state that the tapering schedule is determined by the symptoms of the patient. The Alberta Provincial CNS Tumour Team members recommend that patients should be initially dosed as per surgeon preference with the typical maximum dose being dexamethasone 4 mg four times daily following resection. A slow, fast, or individualized taper may be initiated on the ward and will be continued by the medical and/or radiation oncologist. The “slow taper” is as follows: starting with 4 mg twice daily for 7 days, then 2 mg twice daily for 7 days, then 1 mg twice daily for 7 days then 1 mg once daily for 7 days. The “fast taper” allows for the dexamethasone to be tapered faster and discontinued 3 days following resection.

Following completion of the taper regimen, **symptomatic** patients can be either restarted or continued on a 0.5 mg daily dose of dexamethasone throughout radiotherapy. Patients who have high-grade tumours, are symptomatic, or have a poor life expectancy, can also be maintained on a 0.5-1.0 mg daily dose of dexamethasone following radiotherapy.

All patients should be observed for symptoms of adrenal insufficiency if dexamethasone is discontinued, and advice from an endocrinologist should be sought if needed.

Figure 1 outlines the dexamethasone tapering schedule recommended by members of the Alberta Provincial CNS Tumour Team.
Figure 1. Dexamethasone tapering schedule for adult patients with high-grade gliomas.
Management of Adverse Events Associated with Dexamethasone Therapy

Side effects of steroid therapy occur commonly. Duration of steroid therapy increases the frequency of side effects, and prolonged treatment (>3 weeks) is associated with greater toxicity. Hypoalbuminemia also increases the risk of steroid toxicity, as the percentage of unbound steroid increases, and has been observed in patients with albumin levels less than 25 g/L.

The most common complications of steroid therapy are listed in Table 2, and are discussed in more detail in the sections below.

Table 2. Common complications of steroid therapy.

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Complication</th>
</tr>
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<tbody>
<tr>
<td>Endocrine</td>
<td>hyperglycemia</td>
</tr>
<tr>
<td>Muscular</td>
<td>myopathy</td>
</tr>
<tr>
<td>Skeletal</td>
<td>osteoporosis, avascular necrosis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>peptic ulceration, bowel perforation</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>anxiety, irritability, insomnia, mania, psychosis, depression, seizures</td>
</tr>
<tr>
<td>Infections</td>
<td>Pneumocystic jirovecii pneumonia, candidiasis</td>
</tr>
<tr>
<td>Hematologic</td>
<td>venous thromboembolism</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>hypertension, cardiovascular risk</td>
</tr>
<tr>
<td>General</td>
<td>increased appetite, weight gain, Cushingoid features (moon face, buffalo hump), hirsutism, fragile skin, purpura, acne, striae, hiccups</td>
</tr>
</tbody>
</table>

I. Endocrine Complications

Hyperglycemia has been reported in up to 72% of patients with primary brain tumors receiving dexamethasone. In almost all patients with known diabetes mellitus, glucocorticoid therapy will exacerbate hyperglycemia. Frequently, patients without documented hyperglycemia before corticosteroid therapy are diagnosed with new-onset diabetes mellitus; diabetes induction is related to the glucocorticoid dose and duration, and to the age and body mass index of the patient. The hyperglycemia from corticosteroid therapy usually occurs in the first six weeks of therapy and is believed to be secondary to insulin resistance and increased hepatic gluconeogenesis.

Corticosteroid use typically causes post-prandial hyperglycemia. The peak effect occurs 4 to 6 hours after dosing, and lasts for 13 to 16 hours. For once-daily steroid administration, there is a wearing off effect overnight where blood glucose levels decrease to normal. Argument for the treatment of hyperglycemia due to short-term use of corticosteroids is debatable. The following reasons have been proposed to support treatment of glucocorticoid induced hyperglycemia:

- hyperglycemia may be associated with symptoms such as polyuria, polydipsia, and polyphagia
- infections, such as vulvovaginitis and urinary tract infections, are seen with hyperglycemia
- surgical wound infections may be related to glycemic control
- hyperglycemia may be associated with shorter survival in glioblastoma patients and anaplastic astrocytoma patients

Prevention:

With the high incidence of hyperglycemia during dexamethasone therapy in brain cancer patients, it would seem reasonable to counsel patients on diet and exercise. Health care professionals should advise against the excessive use of snacks, juices and milk as simple carbohydrate sources.
Canada Food Guide, vegetables should be consumed more often than fruit. Patients should be encouraged to enjoy foods with little or no added sugar. Regular exercise is associated with better glycemic control: patients should be advised to exercise for 30 to 45 minutes, four to five times per week.\textsuperscript{21}

**Monitoring and Assessment:**

Diabetics taking glucocorticoids need to perform home glucose monitoring. Random fasting, preprandial and bedtime monitoring done once to twice daily is recommended.\textsuperscript{21} In patients without any previous history of glucose intolerance, fasting blood glucose concentrations will increase slightly, but the major effect of the corticosteroids will be daytime hyperglycemia.\textsuperscript{21} Symptoms of hyperglycemia include:

- increased thirst
- frequent urination
- headaches
- difficulty concentrating
- blurred vision
- fatigue (weak, tired feeling)
- increased hunger
- weight loss

**Treatment:**

Measurement of random glucose levels should be carried out for all patients; fasting glucose levels should also be measured for all patients with random daytime glucose levels above 14 mmol/L. Patients with type 1 diabetes (or type 2 diabetics on insulin) who are on glucocorticoid therapy and have a fasting plasma glucose level lower than 13 mmol/L can be monitored in the oncology clinic in conjunction with their primary care physician; patients who have a fasting plasma glucose level higher than 13 mmol/L should be referred to an endocrinologist/diabetologist. The patient should also be encouraged to interact with a local program offering education and support for diabetes management. For more information, please refer to the Diabetes Programs and Services page of the Alberta Health Services website.

**II. Muscular Complications**

Glucocorticoids have a catabolic effect on skeletal muscle. They lead to muscle atrophy by decreasing protein synthesis and increasing the rate of protein catabolism.\textsuperscript{24} Symptomatic steroid myopathy occurs in approximately 10% of patients, and the incidence is increased in the elderly and after prolonged use of high doses of corticosteroids.\textsuperscript{20} Steroid myopathy is less common in brain cancer patients taking phenytoin, likely due to the induction of hepatic metabolism of dexamethasone by phenytoin resulting in a decreased exposure of the muscle cells to the steroid.\textsuperscript{20} Steroid myopathy can develop in as little as 2 to 3 weeks in patients taking 16 mg of dexamethasone per day.\textsuperscript{17} The development of myopathy correlates best with the total steroid dose.\textsuperscript{17} Steroid myopathy involves proximal muscle weakness and eventual wasting, especially of the pelvic girdle. The proximal arm muscles and neck may become involved as the myopathy progresses. The respiratory muscles may become affected, resulting in symptomatic dyspnea in patients who are severely myopathic.\textsuperscript{17} Serum creatine phosphokinase is usually normal, and electromyography is unremarkable or shows mild myopathic changes. Myopathy is reversible upon discontinuation of the steroid, usually in a few days to several months.\textsuperscript{25}
Prevention:

Myopathy can be prevented by using the lowest possible dose of dexamethasone. Exercise and physiotherapy may attenuate the disorder as demonstrated mainly in animal studies. Steroid myopathy results in loss of both endurance and strength in brain cancer patients; therefore, a program including aerobic exercise and weight training is recommended. Pool exercises and jogging are examples of recommended endurance activities. Resistance training with low weight and high repetitions is generally recommended to prevent ligament, tendon and muscle ruptures. To avoid skin breakdown, repetitive shear forces on the patient’s skin during all types of exercise should be minimized.

Monitoring and Assessment:

Clinical features include proximal and symmetrical muscle weakness and atrophy of the upper and lower extremities, with the quadriceps and other pelvic muscles being more severely affected. Levels of muscle weakness include:

- the patient has difficulty climbing stairs
- the patient cannot rise from a chair
- the patient cannot ambulate independently
- the patient cannot lift extremities against gravity or complete bed mobility skills independently

Evaluation of neck and hip flexor strength allows the most sensitive clinical assessment of steroid myopathy. Estimates of overall endurance can be made with a timed walking or stepping test, or a treadmill. The symptoms of steroid myopathy may be difficult to differentiate from the symptoms of brain tumour progression, or epidural spinal cord compression, paraneoplastic Lambert Eaton myasthenic syndrome and polymyositis or leptomeningeal metastasis.

Treatment:

If a patient is unable to discontinue dexamethasone, lowering the dose or switching medications may reduce the extent of the myopathy. Corticosteroid-induced myopathy is more common with fluorinated corticosteroids (dexamethasone and triamcinolone) compared with non-fluorinated corticosteroids (prednisone or hydrocortisone). Thus, switching from a fluorinated to a non-fluorinated corticosteroid may reduce myopathy. Dexamethasone is the most frequently steroid used in neuro-oncology because of its low mineralocorticoid effects (causing less sodium and water retention), long half-life, and relatively low tendency to induce psychosis. While substituting prednisone for dexamethasone may improve steroid myopathy, it may not be as effective in decreasing brain edema. Treatment of steroid myopathy is difficult and generally limited to physical therapy. Aerobic exercise has been shown to be beneficial in steroid myopathy.

III. Skeletal Complications

Glucocorticoids cause bone loss through many different mechanisms. They reduce intestinal calcium absorption and increase urinary calcium excretion, which stimulates parathyroid hormone production, resulting in increased osteoclast activity and bone resorption. Historically, development of osteoporosis was not a significant problem in malignant glioma patients due to the limited prognosis. With the increase in survival in some of these patients, the complications of osteoporosis, including fractures of the lumbar spine and hip, are becoming more common. Corticosteroids have also been associated with avascular necrosis of the hip or other bones, and may develop after only a few weeks of corticosteroid therapy.
Risk Assessment:

Bone loss from corticosteroid therapy develops within 3 to 6 months, and the fracture risk increases with prednisone doses as low as 2.5-7.5 mg daily. Bone loss during the first 6 months of therapy is approximately 10%, then decreases to 2-5% per year. The risk of hip and vertebral fractures is 2- to 6-fold higher in some patient populations taking corticosteroids. The risk increases with steroid dose, treatment duration, female sex, older age and lower body weight. Patients taking other drugs which are associated with calcium loss, such as loop diuretics, may also be at an increased risk of development of osteoporosis. In addition, patients taking drugs associated with an increased risk of falling, such as antihypertensives, some anticonvulsants and benzodiazepines, may be at an increased fracture risk.

Prevention:

The following recommendations are based on the 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. The reader is encouraged to refer to the Special Groups section of these guidelines, which addresses glucocorticoid-associated bone loss.

Encourage basic bone health including:
- regular active weight-bearing exercise
- calcium (diet and supplements) 1200 mg daily
- vitamin D 800 – 2000 IU daily
- fall prevention strategies

For individuals over the age of 50 who are on long-term glucocorticoid therapy (> 3 months therapy at a prednisone-equivalent dose > 7.5 mg daily) a bisphosphonate (alendronate, risedronate, zoledronic acid) may be initiated at the outset and continued for at least the duration of the glucocorticoid therapy. Bisphosphonates do not reduce fractures in timeframes of less than 6-12 months, so the clinician must consider life expectancy before initiating bisphosphonate therapy. For long-term glucocorticoid users who are intolerant of first-line therapies, calcitonin or etidronate may be considered. Note that the guidelines refer to use of teriparatide for glucocorticoid-induced osteoporosis, but this agent is contraindicated in patients with active malignancy. Note also that bone densitometry is not a pre-requisite for bisphosphonate therapy in patients at high risk of fracture (i.e. over the age of 50 on high dose steroids).

Monitoring and Assessment:

Symptoms of avascular necrosis include:
- pain with use; for example, when the hip is involved, pain is noted especially upon weight-bearing; later, pain may be present at rest
- groin, buttock, thigh or knee pain (when the femur is affected)
- may remain painless

Treatment:

Patients who develop complications should be referred to an endocrinologist or rheumatologist, and to an orthopedic surgeon for compression fractures.
IV. Gastrointestinal (GI) Complications

There is debate over whether steroids cause a higher risk of upper gastrointestinal complications. Two large meta-analyses have been conducted and have reported conflicting results. A review by Messer included 3064 corticosteroid-treated patients evaluated for peptic ulcers. The relative risk of developing peptic ulcers was 2.3 (95% CI 1.4-3.7), and the relative risk of gastrointestinal hemorrhage was 1.5 (95% CI 1.1-2.2). A review by Conn and Poynard yielded statistically insignificant results with a relative risk of 1.3 for peptic ulcers (95% CI 0.8-2.1) and a relative risk of 1.2 for hemorrhage (95% CI 0.7-2.2). The authors noted that the incidence of peptic ulcer tended to increase with the dosage and the duration of therapy. These studies also found that patients using prednisone complained of peptic ulcer-like symptoms more frequently than control patients.

In patients concomitantly receiving NSAIDS, the risk of peptic ulcers is four to seven times higher. The incidence of ulcers and bleeding is higher in patients using anticoagulants and in patients who have a history of upper GI bleeding. Bowel perforation is also a serious complication of corticosteroid therapy. It tends to occur in patients treated with high doses of steroids who have been constipated due to medication, immobility or neurologic dysfunction.

Prevention:

**Peptic ulcers and GI hemorrhage:** There is no evidence to support the co-administration of an H2 blocker, an antacid, or a proton pump inhibitor with dexamethasone to lower the incidence of gastrointestinal ulceration. A survey of Canadian neurosurgeons revealed that 94 of 102 respondents (92.2%) co-prescribed prophylaxis against GI complications when administering dexamethasone. The most commonly drug prescribed was ranitidine (83.3% of respondents). None of the physicians were able to offer any data to support this practice. Twenty-five physicians (24.5%) stated that this was standard practice or taught to them as a resident. The NCCN guidelines advise that patients with high risk of GI side effects such as peri-operative patients, prior history of ulcers/GI bleed, receiving NSAIDS, or anticoagulation should receive H2 blockers or proton pump inhibitors. Wen and colleagues advise that the use of H2 blockers and proton pump inhibitors in brain tumour patients should be restricted to the peri-operative period and to patients receiving “high doses” of corticosteroids. They further recommend that for most other patients, prophylactic therapy is unnecessary unless they are at high risk for developing peptic ulceration (i.e., patients with a previous history of peptic ulceration, receiving anticoagulation or NSAIDS, and the elderly). As proton pump inhibitors and misoprostol 200 ug three times daily are more effective than H2 blockers in preventing NSAID-induced ulcers, patients receiving NSAIDS and dexamethasone should use one of these agents. Although there is conflicting data, and controversy exists regarding the definition of “high doses”, the Alberta Provincial CNS Tumour Team members recommend the use of H2 blockers for all patients with high-grade gliomas who are treated with dexamethasone, unless there is a contraindication. The use of H2 blockers and proton pump inhibitors in other patients is at the discretion of the prescriber.

**Bowel perforation:** Prevention of constipation is important in preventing bowel perforation. There must be adequate bulk in the diet, increased fluid intake, and use of laxatives as necessary. The best evidence for laxative efficacy is with the polyethylene glycol (PEG) products, Lax-a-Day and RestoraLax. These products have the added advantages of being tasteless and causing minimal cramping. If use of a PEG product is not effective, the next best evidence is for use of Lactulose.
Table 5. Common laxatives for prevention of constipation and bowel perforation.

<table>
<thead>
<tr>
<th>PEG 3350</th>
<th>Lactulose</th>
</tr>
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<tbody>
<tr>
<td>• Lax-a-Day or RestoraLax powder</td>
<td>• Dose: 15 mL PO qhs. Increase by 15 mL q3h until</td>
</tr>
<tr>
<td>• Dose: 17 g in 8 oz juice/water po qhs.</td>
<td>cramps begin and bowel movement is achieved, then</td>
</tr>
<tr>
<td>• Onset of action is 24-72 hours.</td>
<td>stop. Divide the total dose up to that point by one to</td>
</tr>
<tr>
<td>• Doses can be given once daily (e.g. 2 x 17g dissolved</td>
<td>three times daily, and use as tolerated to target BM q1-</td>
</tr>
<tr>
<td>8 oz. liquid and taken nightly) or divided, depending</td>
<td>2 days.</td>
</tr>
<tr>
<td>on patient preference</td>
<td>• Onset of action is 24-48 hours.</td>
</tr>
<tr>
<td></td>
<td>• Some patients may find the sweet taste intolerable.</td>
</tr>
</tbody>
</table>

Monitoring and Assessment:

Symptoms of peptic ulcer disease (PUD):
- gnawing or burning epigastric pain
  - the pain may awaken the patient at night or between meals when the stomach is empty
  - the pain is usually relieved with food or antacids
- nausea
- loss of appetite, bloating, feeling of fullness

Symptoms of complicated PUD (requiring immediate medical attention):
- vomiting (may indicate obstruction)
- melena or hematemesis/coffee ground vomitus (GI bleeding)
- severe abdominal pain (perforation)

Treatment:
- Rectal exam, CBC and fecal occult blood test are recommended to rule out bleeding
- H. pylori test (blood or breath test) is recommended to rule out H. pylori
- Proton pump inhibitors are the drugs of choice in managing patients with peptic ulcers, including NSAID-induced ulcers. Proton pump inhibitors have equivalent clinical efficacy at standard doses
  - Lansoprazole
    - GU: 30 mg daily ac x 4-8 weeks
    - DU: 30 mg daily ac x 2-4 weeks
  - Omeprazole
    - GU: 20 mg daily ac x 4-8 weeks
    - DU: 20 mg daily ac x 2-4 weeks
  - Pantoprazole
    - GU: 40 mg daily ac x 4-8 weeks
    - DU: 40 mg daily ac x 2-4 weeks
- Patients who test positive for H. pylori should receive triple therapy with a proton pump inhibitor + amoxicillin + clarithromycin or a proton pump inhibitor + metronidazole + clarithromycin. Alternately, quadruple therapy with a proton pump inhibitor + bismuth + metronidazole + tetracycline may be used.

V. Psychiatric Complications

Mild psychiatric effects of steroids include anxiety, irritability and insomnia. The incidence of these side effects ranges from 13 to 62%. Severe manifestations include mania, depression and psychosis. The incidence of severe reactions is 5.7% (range 1.6 to 50%). Most psychiatric reactions occur within the first week of steroid therapy, and the most significant risk factor associated with psychiatric reactions is
the corticosteroid dose. Resolution of delirium can occur within days, whereas recovery from depression or mania may take up to 6 weeks. Corticosteroids can also cause cognitive impairment such as memory disturbances. Cognitive deficits are dose dependent and resolve on termination of the corticosteroid.

**Prevention:**

Recommendations for prevention of insomnia include:

- Use the lowest possible corticosteroid dose
- Nap for only 20 minutes at a time during the day
- Establish a regular sleep/rest pattern
- Avoid smoking, alcohol and/or caffeinated drinks before sleep
- Do not do vigorous exercise before bedtime
- Meditation, warm baths and music may help

**Monitoring and Assessment:**

The NCCN Distress Management Guidelines recommend regularly using a screening tool to identify a patient’s level of distress. A rating scale (for example, from 0 to 10) can be used to identify the level of a patient’s distress. The term “distress” is defined as a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social and/or spiritual nature that may interfere with the ability to cope effectively with cancer. This term is used instead of “psychological” or “psychiatric” which are felt to be stigmatizing terms. The Alberta Provincial CNS Tumour Team members follow the recommendations of the Pan-Canadian Practice Guideline for Screening, Assessment, and Care of Psychosocial Distress (Depression, Anxiety) for Adults with Cancer. This guideline recommends the use of the Screening for Distress tool, incorporating the Edmonton Symptom Assessment System (ESAS), which enables a patient to rank being tired, depressed or anxious from 0 (symptom not present) to 10 (worst possible), as well as the Canadian Problem Checklist. Persistent feelings of dysphoria, hopelessness, helplessness, loss of self-esteem, feelings of worthlessness and suicidal ideation are aspects of a psychiatric illness. Mental health professionals are required to conduct thorough examinations of patients, using the DSM-IV-TR as a reference.

**Treatment:**

If a patient’s stress is moderate or severe, prompt referral to a mental health professional, social worker or spiritual counselor is recommended based on the problem causing the distress. Any patient recognized as possibly suicidal must be referred for immediate psychological assessment. Non-pharmacologic therapy of distress includes cognitive behavioral therapy, intensive psychotherapy, and group therapy. Studies have shown that anti-depressants and anti-anxiety drugs are beneficial in the treatment of depression and anxiety in adult cancer patients.

**Insomnia:** Recommended sedatives for insomnia include:

- Zopiclone (a cyclopyrrolone)
  - initial dose 5 mg daily, maximum 20 mg daily
  - onset of action 30 minutes
- Temazepam (benzodiazepine)
  - initial dose 15 mg daily, maximum 60 mg daily
  - good benzodiazepine choice, but all benzodiazepines are associated with increased falls and fractures, dizziness and un-coordination
Both zopiclone and temazepam are associated with dependence.\textsuperscript{36}

\textbf{Anxiety:} The NCCN Guidelines recommend psychotherapy with or without an anxiolytic or an antidepressant in the treatment of anxiety, after eliminating medical causes.\textsuperscript{36} Please see antidepressant and anxiolytic agents listed under depression section below.

\textbf{Depression:} The NCCN guidelines recommend psychotherapy and an antidepressant with or without an anxiolytic for the treatment of mood disorders.\textsuperscript{36} The choice of an antidepressant is mainly based on the side effect profile and drug interaction potential, as no single antidepressant appears to be significantly more efficacious than the others.\textsuperscript{39} Paroxetine and mirtazapine are more sedating, and sertraline and venlafaxine are more activating. Bupropion should not be used in neuro-oncology as it lowers the seizure threshold. Tricyclic antidepressants are not recommended in patients with brain tumours experiencing psychiatric effects of steroids, as they may confound the problem.\textsuperscript{20}

\textbf{Table 6.} Common antidepressants and anxiolytics.

<table>
<thead>
<tr>
<th>Selective Serotonin Reuptake Inhibitors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine</td>
<td>initial dose 20 mg daily, maximum dose 50 mg daily</td>
</tr>
<tr>
<td>Sertraline</td>
<td>initial dose 50 mg daily, maximum dose 200 mg daily</td>
</tr>
<tr>
<td>Citalopram</td>
<td>initial dose 20 mg daily</td>
</tr>
<tr>
<td></td>
<td>caution in patients receiving ondansetron as both agents prolong the QT interval and the combination may cause ventricular arrhythmias</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>initial dose 20 mg daily, maximum dose 80 mg daily</td>
</tr>
<tr>
<td></td>
<td>caution in patients receiving ondansetron as both agents prolong the QT interval and the combination may cause ventricular arrhythmias</td>
</tr>
</tbody>
</table>

| Serotonin Norepinephrine Reuptake Inhibitors |  |
| Venlafaxine                                | initial dose 37.5-75 mg daily, maximum dose 225 mg daily |

<table>
<thead>
<tr>
<th>Alpha-2 Antagonist</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirtazapine</td>
<td>initial dose 15 mg nightly, maximum dose 45 mg daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anxiolytics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxazepam</td>
<td>short acting benzodiazepine*</td>
</tr>
<tr>
<td></td>
<td>initial dose 10 mg daily, maximum dose 120 mg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>short acting benzodiazepine*</td>
</tr>
<tr>
<td></td>
<td>initial dose 0.5 mg daily, maximum dose 10 mg</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>long acting benzodiazepine*</td>
</tr>
<tr>
<td></td>
<td>initial dose 0.25 mg daily, maximum dose 10 – 20 mg</td>
</tr>
<tr>
<td>Buspirone (azapirone)</td>
<td>initial dose 5 mg daily, maximum dose 69 – 90 mg</td>
</tr>
<tr>
<td></td>
<td>Onset of efficacy is one week, maximum effect at 6 weeks</td>
</tr>
<tr>
<td></td>
<td>No dependence, non-addicting</td>
</tr>
</tbody>
</table>

*Benzodiazepines are especially useful for the first month of anxiety and antidepressant therapy while waiting for the antidepressants to work. Long acting benzodiazepines have less rebound anxiety and withdrawal. To avoid withdrawal, taper the doses of antidepressants and anxiolytics.

\textbf{Psychosis:} Discontinuing or tapering the dexamethasone should be attempted, if possible. Neuroleptics and lithium may be considered in consultation with a psychiatrist.

\textbf{VI. Infections}

Corticosteroids are immunosuppressive and result in opportunistic infections in patients taking moderate to high doses of dexamethasone. Patients whose CD4 counts drop below 200 cells per cubic millimeter are especially vulnerable to infection.\textsuperscript{20} The opportunistic infections seen in brain cancer patients include
Pneumocystic jirovecii pneumonia (PJP, formerly pneumocystic carinii pneumonia or PCP), and Candida mucositis and esophagitis. The incidence of PJP may also be increased in patients receiving temozolomide therapy for malignant gliomas. The rate of PJP in patients with brain tumours is estimated to be 1 to 6%. Most patients who develop PJP have been on steroid therapy for prolonged periods (greater than 2 months) and infection with PJP was more likely to occur during the steroid taper.

Prevention:

PJP: It may be prudent to consider prophylactic therapy against PJP in brain cancer patients receiving prolonged corticosteroid therapy. Trimethoprim-sulfamethoxazole (TMP-SMX) is very effective in preventing PJP administered either as a single dose daily (“DS” or 160 mg trimethoprim plus 800 mg sulfamethoxazole) or 3 days a week. For patients allergic to sulfa drugs or trimethoprim, aerosolized pentamidine, dapsone or atovaquone are effective alternatives.

### Table 7. PJP prophylaxis doses

<table>
<thead>
<tr>
<th>Prophylaxis Method</th>
<th>Dose Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>DS (sulfamethoxazole 800 mg + trimethoprim 160 mg) three times weekly or SS (sulfamethoxazole 400 mg + trimethoprim 80 mg) daily</td>
</tr>
<tr>
<td>aerosolized pentamidine</td>
<td>300 mg monthly (in 6 ml sterile water)</td>
</tr>
<tr>
<td>dapsone</td>
<td>50 mg twice daily or 100 mg daily</td>
</tr>
<tr>
<td>atovaquone</td>
<td>1500 mg daily with food</td>
</tr>
<tr>
<td>dapsone + pyrimethamine + leucovorin</td>
<td>Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg, once weekly</td>
</tr>
</tbody>
</table>

Drug interactions: Dexamethasone may increase elimination of trimethoprim and dapsone, due to induction of the CYP3A4 enzyme. The clinical significance of this interaction is unknown. Phenytoin serum concentrations may be increased by trimethoprim. In healthy volunteers, administration of trimethoprim (320 mg/day for 7 days) increased the half-life of phenytoin (single IV dose) by 51%. Two case reports of phenytoin toxicity in patients receiving trimethoprim/sulfamethoxazole have been published. Phenytoin may increase elimination of dapsone and pentamidine.

Monitoring and Assessment:

- Follow lymphocyte counts
- Symptoms of PJP:
  - cough
  - fever
  - increased respiratory rate
  - shortness of breath, especially on exertion
  - fatigue
  - chest pain
- Lactate dehydrogenase levels are usually elevated; a chest x-ray is also recommended in the diagnosis of PJP
- Symptoms of Candida mucositis:
  - White, slightly raised lesions on the tongue and inner cheeks (sometimes the roof of the mouth, gums and tonsils)
  - uncomfortable burning sensation in the mouth and throat
  - slight bleeding if lesions are rubbed or scraped
  - cracking and redness at the corners of the mouth
  - cottony feeling in the mouth
  - loss of taste
• Symptoms of Candida esophagitis:
  o difficulty swallowing
  o feeling like food is getting stuck in the throat

Treatment:

Table 8. Treatment of infections associated with steroid use.²⁰,⁴¹

<table>
<thead>
<tr>
<th>PJP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>trimethoprim-sulfamethoxazole</td>
<td>po: 2 DS tabs every 8 hours x 21 days</td>
</tr>
<tr>
<td></td>
<td>IV: sulfamethoxazole 25 mg/kg and trimethoprim 5 mg/kg every 8 hours x 21 days</td>
</tr>
<tr>
<td></td>
<td><em>Prednisone should also be given 15-30 minutes before TMP-SMX: 40 mg twice daily x 5 days, then 40 mg daily x 5 days, then 20 mg daily for 11 days (Gilbert 2011).</em></td>
</tr>
<tr>
<td>trimethoprim + dapsone</td>
<td>trimethoprim po 320 mg or 5 mg/kg three times daily + dapsone 100 mg daily x 21 days</td>
</tr>
<tr>
<td>atovaquone suspension</td>
<td>po 750 mg twice daily with food x 21 days</td>
</tr>
<tr>
<td>clindamycin + primaquine</td>
<td>clindamycin po 300-450 mg po every 6 hours OR IV 600 mg every 8 hours + primaquine 30 mg po daily x 21 days</td>
</tr>
<tr>
<td>pentamidine</td>
<td>4 mg/kg/day IV x 21 days</td>
</tr>
</tbody>
</table>

Oropharyngeal Candidiasis

| Nystatin 100,000 U/mL suspension | 500,000 (5 mL) four times daily x 7 days or 2 days after improvement. Swish and swallow. |
| Fluconazole 100 mg tab           | Load: 200 mg po x 1 → 100 mg po daily x 7 days                  |
| Itraconazole (if fluconazole resistant) 10 mg/mL solution | 200 mg po once daily of solution x 14 days                        |

Esophageal Candidiasis

| Fluconazole 100 mg tab | 200 – 400 mg daily x 2-3 weeks |
| Itraconazole (if fluconazole resistant) | 200 mg po daily of solution x 14-21 days |

VII. Hematologic Complications

High-dose dexamethasone treatment may have a prothrombotic effect and contribute to the increased risk of venous thromboembolism (VTE) in brain cancer patients.⁹,²⁰,⁴⁰ VTE is a common complication of brain tumours, with an incidence of 30% in high-grade glioma patients.¹

Prevention for Ambulatory Cancer Patients Receiving Chemotherapy:

As per the ASCO Guidelines for VTE prophylaxis in patients with cancer, routine prophylaxis with an antithrombotic agent is not recommended.⁴² The 2011 NCCN guidelines give an option of prophylaxis in individuals considered to be at risk of VTE based on assessment of VTE risk factors, but state that prospective randomized data are needed to assess the benefit and safety of routine VTE prophylaxis in a cancer outpatient population with a favorable risk-benefit ratio.⁴³ The agents recommended for prophylaxis include low molecular weight heparin (LMWH; dalteparin, enoxaparin, tinzaparin), fondaparinux, unfractionated heparin and warfarin. The NCCN guidelines also state that aspirin should not be used in non-myeloma patients for VTE prevention.⁴³ There is no evidence to support the use of graduated compression stockings as the sole method of VTE prophylaxis in cancer patients.
Two trials investigating primary prophylaxis of malignant glioma patients with LMWH have not been able to demonstrate with statistical significance a reduction in VTE and have shown occurrence of CNS hemorrhage.\textsuperscript{44,45}

**Monitoring and Assessment:**

The symptoms of deep venous thrombosis (DVT) include:
- Swelling in one or both legs
- Pain or tenderness in one or both legs, which may occur only while standing or walking
- Warmth of the skin of the affected leg
- Red or discolored skin in the affected leg
- Visible surface veins

DVT usually involves the deep veins of the legs or arms. It may cause life-threatening emboli to the lungs and valvular dysfunction and chronic leg swelling. The classic symptoms of pain and swelling may be present or absent, unilateral or bilateral, mild or severe. When obstruction is high (for example, in the pelvic veins), edema may be bilateral. Leg pain is only present in 50% of patients and doesn’t correspond to the location of the thrombus. When tenderness is present, it is usually confined to the calf muscles or along the deep veins in the medial thigh. Warmth and erythema may be present over the area of the thrombus.

The symptoms of pulmonary embolism are:
- sudden onset of cough
- sharp chest pain
- rapid breathing or shortness of breath
- lightheadedness

Suspicion of a DVT or pulmonary embolism is a medical emergency and requires immediate medical attention.

**Treatment:**

The 2007 ASCO Guidelines for treatment of venous thromboembolism states that LMWH is the preferred approach for cancer patients with established VTE.\textsuperscript{42} The guidelines also recommend LMWH as the preferred approach for long-term anticoagulant therapy. For patients with CNS malignancies, the guidelines recommend careful monitoring for hemorrhagic complications, and state that anticoagulation be avoided in the presence of active intracranial bleeding, recent surgery, pre-existing bleeding diathesis such as thrombocytopenia (platelet count < 50,000/uL) or coagulopathy.\textsuperscript{42} The 2011 NCCN guidelines for VTE treatment include unfractionated heparin (UFH), LMWH or fondaparinux for acute treatment upon diagnosis of VTE.\textsuperscript{43} The guidelines state that since chronic therapy with LMWH is associated with superior outcomes in cancer patients with VTE, its use in the acute phase may be preferable. For chronic management of VTE, the NCCN guidelines recommend LMWH for the first six months for treatment of proximal DVT or PE. After six months, there is the option to switch to warfarin therapy. Wen and colleagues state a preference for LMWH over warfarin because of increased effectiveness in preventing VTE, the lack of interaction with other drugs, and the convenience of not having to monitor the INR.\textsuperscript{46} Long term anticoagulation is recommended for patients with malignant gliomas.\textsuperscript{20}
Table 9. LMWH dosing.43,47-50

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>200 U/kg sc daily x 30 days, then 150 U/kg sc daily</td>
</tr>
<tr>
<td></td>
<td>Although each of the LMWHs have been studied in randomized controlled trials in cancer patients, the efficacy of dalteparin in this population is supported by the highest quality evidence and is the only LMWH approved by Health Canada for this indication</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1 mg/kg sc every 12 hours</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>175 U/kg sc daily</td>
</tr>
<tr>
<td></td>
<td>Tinzaparin should be avoided in patients over 70 years of age with renal insufficiency.</td>
</tr>
</tbody>
</table>

It is important to note that the NCCN guidelines panel recognizes current evidence suggesting caution should be used when administering LMWHs to patients with ClCr < 50 mL/min.43

VIII. Cardiovascular Complications

Corticosteroids have been associated with hypertension. A meta-analysis of randomized, double-blind controlled trials revealed an OR of 2.2 (95% CI 1.4, 3.8).32 The mechanism for the increase in blood pressure is unknown; in addition, the risk factors for corticosteroid-induced hypertension are unknown, although some authors report that the risk is dose dependant.26 Two large observational studies in the literature evaluated the correlation between systemic corticosteroids and cardiovascular disease.51,52 The first study revealed an increased risk of cardiovascular or cerebrovascular events (OR 1.25; 95% CI 1.21, 1.29).51 The second study revealed a higher risk of cardiovascular events (OR 2.56; 95% CI 2.18, 2.99).52

There is no clear evidence regarding prevention and treatment of corticosteroid-induced hypertension. Screening for corticosteroid-induced hypertension, particularly during the first months of therapy and in patients with corticosteroid-induced lipodystrophy is recommended.26

IX. Additional Complications

Additional toxicities not already addressed may include:
- Low albumin levels have been associated with increased toxicity from steroid therapy in brain cancer patients.18 Optimizing patient nutrition by encouraging a diet containing adequate protein is recommended.15
- Increased appetite, weight gain, Cushingoid features (moon face, buffalo hump)
  - patients may experience distress due to temporary weight gain and “moon face” from steroid use.
  - patients should be encouraged to exercise regularly, and discouraged from dieting.
- Chronic, supraphysiologic glucocorticoid use has been associated with hypogonadism which may manifest as amenorrhea in premenopausal women or low testosterone in men. Although there is no data specific to brain tumours other than pituitary tumours, in other populations is it known that hypogonadism may be associated with hot flashes, low libido and fatigue. In older men, even short term treatment of symptomatic hypogonadism has been shown to improve quality of life.53 Testosterone may reduce dexamethasone induced myopathy.54,55 We recommend that free testosterone levels be measured in all patients with high grade gliomas who are receiving dexamethasone. A baseline measurement should be taken prior to starting radiotherapy and then again during the adjuvant chemotherapy phase of treatment. For male patients, free testosterone should be measured monthly. Patients with low free testosterone levels and symptomatic hypogonadism who are appropriate candidates for possible hormone replacement may be referred to an endocrinologist. There is a need
for further research in this population to better define potential candidates and measure quality of life outcomes with such hormone therapy.

- Hirsutism
- Fragile skin
- Purpura
- Acne
- Striae
- Hiccups

- physical measures to relieve hiccups should be attempted first, although the efficacy of these measures is only evidenced by case reports:\(^\text{56}\)
  - breath holding
  - stimulating nasopharynx or uvula (sipping cold water, gargling with water, swallowing a teaspoon of dry sugar)
  - vagal stimulation (for example, pressing on the eyeballs)
  - counter-irritation of the diaphragm (for example, pulling the knees to the chest

- pharmacologic measures to relieve hiccups include:\(^\text{56}\)
  - chlorpromazine: 25 mg three times daily, up to 7 to 10 days; maximum dose 50 mg four times daily
  - metoclopramide: 10 mg three to four times daily for 7 to 10 days
GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BID</td>
<td>twice daily</td>
</tr>
<tr>
<td>CI</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>DVT</td>
<td>deep venous thrombosis</td>
</tr>
<tr>
<td>ESAS</td>
<td>Edmonton Symptom Assessment System</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>LMWH</td>
<td>low molecular weight heparin</td>
</tr>
<tr>
<td>HPA</td>
<td>hypothalamic-pituitary-adrenocortical</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>NPH</td>
<td>neutral protamine Hagedorn insulin</td>
</tr>
<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PEG</td>
<td>polyethylene glycol</td>
</tr>
<tr>
<td>PJP</td>
<td>Pneumocystis jirovecii pneumonia</td>
</tr>
<tr>
<td>PPG</td>
<td>post-prandial glucose</td>
</tr>
<tr>
<td>PUD</td>
<td>peptic ulcer disease</td>
</tr>
<tr>
<td>QID</td>
<td>four times daily</td>
</tr>
<tr>
<td>VTE</td>
<td>venous thromboembolism</td>
</tr>
<tr>
<td>WBRT</td>
<td>whole brain radiotherapy</td>
</tr>
</tbody>
</table>

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2013. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial CNS Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial CNS Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES


40. Lexicomp (TM). Lexi-Drugs. 2010;1.7.3(151).
47. Lexicomp (TM). Lexi-Drugs: enoxaparin monograph. 2010;1.7.3(151).