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The Use of Dexamethasone in Patients with High-Grade Gliomas

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Background

Patients with primary brain tumours often develop vasogenic edema and increased intracranial pressure. Corticosteroid therapy improves this in most patients, generally within 48 hours.[1] As such, corticosteroid therapy is sometimes a necessary prerequisite to embarking on chemotherapy and radiotherapy following surgery, particularly in patients whose brain tumours exert 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.

Guideline Questions

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

Search Strategy

Medical journal articles were searched using the Medline (1948 to April Week 4 2020), PubMed (1950-April 2020), Cochrane Database of Systematic Reviews (2005 to April 2020), 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 ECRI Guidelines Trust 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

The following recommendations apply to adult cancer patients with high-grade gliomas.

Recommendations

1. Treatment with the lowest possible dexamethasone dose is recommended for symptom relief in patients with primary high-grade gliomas and cerebral edema. (Level of Evidence: III, Strength of Recommendation: C).
2. Following surgery, a maximum dose of 16 mg daily, administered in twice-daily doses is recommended for symptomatic patients. (Level of Evidence: II, Strength of Recommendation: B).

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.

Guideline Developer	Recommendations
NCCN, 2020[2]	• In general the lowest dose of steroids should be used for the shortest time possible. • Downward titration of the dose should be attempted whenever possible.
BC Cancer Agency, 2020[3]	• 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. • 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.
Neurosurgery 2019[4]	• Corticosteroids are recommended to provide temporary symptomatic relief of symptoms related to increased intracranial pressure and edema secondary to brain metastases. • If corticosteroids are given, dexamethasone is the best drug choice given the available evidence. • Corticosteroids, if given, should be tapered as rapidly as possible but no faster than clinically tolerated, based upon an individualized treatment regimen and a full understanding of the long-term sequelae of corticosteroid therapy.
Neuro-oncology 2018[5]	• No Dexamethasone is recommended during radiotherapy or chemotherapy unless the patient is symptomatic.
ESMO 2014[6]	• Corticosteroids (usually dexamethasone 8–16 mg/day, but lower doses may be just as effective) allow for rapid reduction of tumour-associated edema and improve clinical symptoms.

Australian Cancer Network, 2013[7]	• The usual starting dose is 16mg per day. • The dose of dexamethasone should be gradually tapered to the lowest amount that controls the patient's symptoms; dexamethasone should not be discontinued abruptly.
American College of Radiology, 2013[8]	• 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. • In all cases, steroids should be tapered as clinically indicated and tolerated.

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.[9] 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.[9]

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.[10] 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.[11] 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.[11]

The majority of retrospective studies and reviews report the most common starting dose of dexamethasone to be between 8 and 16 mg per day.[9,12-14] 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.[15] 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.[16,17]

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 two equal daily doses, for symptomatic patients following biopsy or surgical resection.

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 4 mg daily for 7 days, then 2 mg once 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.

Dexamethasone shortage

If the dexamethasone prescription cannot be filled due to a shortage (utilizing multiple strengths, if necessary) – the following equivalent dosing with prednisone is recommended.[18,19]

Table 2. Titrated dose of Prednisone as compare to Dexamethasone

Dexamethasone Dose	Equivalent Dose of Prednisone
4 mg	25 mg
8 mg	50 mg
10 mg	50 mg
12 mg	75 mg
16 mg	100 mg
20 mg	125 mg

Prednisone has less glucocorticoid/anti-inflammatory effects than dexamethasone, so the prednisone dose may need to be titrated. Prednisone also has more mineralocorticoid/salt-retaining effects than dexamethasone, so use caution in patients at risk for fluid overload.

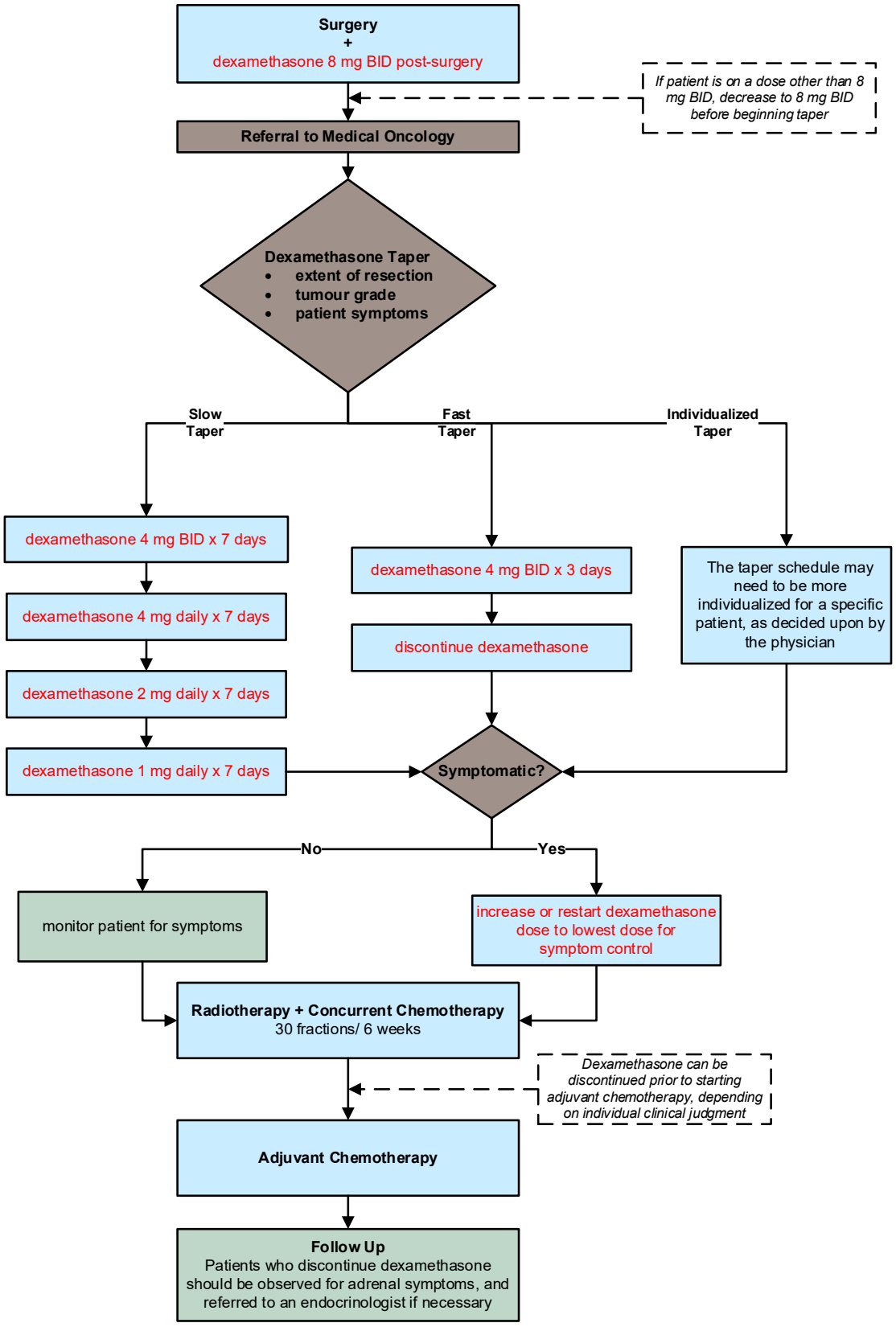
Most patients begin to improve symptomatically within hours of dexamethasone administration, and achieve a maximum benefit within 24 to 72 hours.[16] There is a high-rate of side-effects associated with prolonged dexamethasone use, as well as a risk of suppression of the hypothalamic-pituitary-adrenocortical (HPA) axis; therefore, dexamethasone should be tapered once symptoms begin to improve.[16-17,20] 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.[3,9-11,15] 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.[21,22] Other publications state that the tapering schedule is determined by the symptoms of the patient.[2,7-8] 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 8 mg twice 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 4 mg once daily for 7 days, then 2 mg once 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.



4. 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. (Level of Evidence: I, Strength of Recommendation: A)

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.[22] 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.[23]

The most common complications of steroid therapy are listed in Table 3, and are discussed in more detail in the sections below.[23]

Table 3. Common complications of steroid therapy

Organ System	Complication
Endocrine	hyperglycemia
Muscular	myopathy
Skeletal	osteoporosis, avascular necrosis
Gastrointestinal	peptic ulceration, bowel perforation
Psychiatric	anxiety, irritability, insomnia, mania, psychosis, depression, seizures
Infections	Pneumocystic jirovecii pneumonia, candidiasis
Hematological Complications	Venous thromboembolism
Cardiovascular	hypertension, cardiovascular risk
General	increased appetite, weight gain, Cushingoid features (moon face, buffalo hump), hirsutism, fragile skin, purpura, acne, striae, hiccups

I. Endocrine Complications

Hyperglycemia has been reported in up to 72% of patients with primary brain tumours receiving dexamethasone.[12] In almost all patients with known diabetes mellitus, glucocorticoid therapy will exacerbate hyperglycemia.[24] 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.[24] 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.[25]

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[26]

- infections, such as vulvovaginitis and urinary tract infections, are seen with hyperglycemia[26]
- surgical wound infections may be related to glycemic control[26]
- hyperglycemia may be associated with shorter survival in glioblastoma patients and anaplastic astrocytoma patients[27,28]

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.[26] As per the 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.[26]

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.[26] 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.[26] 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.[29] 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.[25] 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.[25] Steroid myopathy can develop in as little as 2 to 3 weeks in patients taking 16 mg of dexamethasone per day.[22] The development of myopathy correlates best with the total steroid dose.[22] 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.[22] Serum creatinine 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.[30]

Prevention:

Myopathy can be prevented by using the lowest possible dose of dexamethasone.[25] Exercise and physiotherapy *may* attenuate the disorder as demonstrated mainly in animal studies.[25,29,31] 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.[32] 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.[32] To avoid skin breakdown, repetitive shear forces on the patient's skin during all types of exercise should be minimized.[32]

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.[30] Levels of muscle weakness include:[32]

- 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.[21] Estimates of overall endurance can be made with a timed walking or stepping test, or a treadmill.[21] 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.[33]

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.[16] While substituting prednisone for dexamethasone may improve steroid myopathy, it may not be as effective in decreasing brain edema.[16] Treatment of steroid myopathy is difficult and generally limited to physical therapy.[25] Aerobic exercise has been shown to be beneficial in steroid myopathy.[30]

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.[34] 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.[25] 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.[21]

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.[35] Bone loss during the first 6 months of therapy is approximately 10%, then decreases to 2-5% per year.[31] The risk of hip and vertebral fractures is 2- to 6- fold higher in some patient populations taking corticosteroids.[31] The risk increases with steroid dose, treatment duration, female sex, older age and lower body weight.[31] 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.[17] 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.[17]

Prevention:

The following recommendations are based on the 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada.[35] 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 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.[36] 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).[37] 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.[34]

In patients concomitantly receiving NSAIDS, the risk of peptic ulcers is four to seven times higher.[31] The incidence of ulcers and bleeding is higher in patients using anticoagulants and in patients who have a history of upper GI bleeding.[22] Bowel perforation is also a serious complication of corticosteroid therapy.[22] 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.[38] 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.[2] 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.[25] 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 mcg orally 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.[39]

Bowel perforation: The complication of corticosteroid therapy that tends to occur in patient receiving high doses of steroids and who have been constipated either due to medication, immobility or neurological dysfunction. 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.[22] 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 4. Common laxatives for prevention of constipation and bowel perforation

PEG 3350	Lactulose
• Lax-a-Day or RestoraLax powder • Dose: 17 g in 8 oz juice/water po qhs. Increase by 17 g/day or as tolerated to target BM q1-2 days. • Onset of action is 24-72 hours.	• Dose: 15 mL PO qhs. Increase by 15 mL q3h until cramps begin and bowel movement is achieved, then stop. Divide the total dose up to that point by one to three times daily, and use as tolerated to target BM q1-2 days.

• Doses can be given once daily (e.g. 2 x 17g dissolved in 8 oz. liquid and taken nightly) or divided, depending on patient preference	• Onset of action is 24-48 hours. • Some patients may find the sweet taste intolerable.

Monitoring and Assessment:

Symptoms of peptic ulcer disease (PUD) include:

- 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 is restricted to areas with known low clarithromycin resistance or high eradication success with these regimens. Alternately, quadruple therapy with a proton pump inhibitor + bismuth + metronidazole + tetracycline or first-line strategies which include concomitant nonbismuth quadruple therapy (proton pump inhibitor [PPI] + amoxicillin + metronidazole + clarithromycin [PAMC]) 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%.[34] Severe manifestations include mania, depression and psychosis. The incidence of severe reactions is 5.7% (range 1.6 to 50%).[34] 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.[34] Resolution of delirium can occur within days, whereas recovery from depression or mania may take up to 6 weeks.[34] Corticosteroids can also cause cognitive impairment such as memory disturbances. Cognitive deficits are dose dependent and resolve on termination of the corticosteroid.[34]

Prevention:

Recommendations for prevention of insomnia include:[40]

- 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.[41] 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.[41] 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.[42] 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 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.[41]

Insomnia: Recommended sedatives for insomnia include:

- Zopiclone (a cyclopyrrolone)
  - initial dose 3.75 mg orally at bedtime daily, maximum 7.5 mg orally at bedtime daily
  - onset of action 30 minutes[43]
- 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[43]

Both zopiclone and temazepam are associated with dependence.[43]

Anxiety: The NCCN Guidelines recommend psychotherapy with or without an anxiolytic or an antidepressant in the treatment of anxiety, after eliminating medical causes.[41] Please see antidepressant and anxiolytic agents listed under depression section below.

Depression: The NCCN guidelines recommend psychotherapy and an antidepressant with or without an anxiolytic for the treatment of mood disorders.[41] 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.[44] Paroxetine and mirtazapine are more sedating, and sertraline and venlafaxine are more activating. Buproprion 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.[25]

Table 5. Common antidepressants and anxiolytics.

Antidepressants[45]	
Selective Serotonin Reuptake Inhibitors	
Paroxetine	initial dose 20 mg daily, maximum dose 10-20 mg daily
Sertraline	initial dose 50 mg daily, maximum dose 25-50 mg daily
Citalopram	• initial dose 10-20 mg daily • caution in patients receiving ondansetron as both agents prolong the QT interval and the combination may cause ventricular arrhythmias
Fluoxetine	• initial dose 10-20 mg daily, maximum dose 80 mg daily • caution in patients receiving ondansetron as both agents prolong the QT interval and the combination may cause ventricular arrhythmias
Serotonin Norepinephrine Reuptake Inhibitors	
Venlafaxine	initial dose 37.5 mg daily, maximum dose 225 mg daily
Alpha-2 Antagonist	
Mirtazapine	initial dose 7.5 mg nightly, maximum dose 45 mg daily
Anxiolytics[38]	
Oxazepam	• short acting benzodiazepine* • initial dose 10 mg daily, maximum dose 120 mg
Lorazepam	• short acting benzodiazepine*

	• initial dose 0.5 mg daily, maximum dose 10 mg
Clonazepam	• long acting benzodiazepine* • initial dose 0.25 mg daily, maximum dose 10 – 20 mg
Buspirone (azapirone)	• initial dose 5 mg daily, maximum dose 60 – 90 mg • Onset of efficacy is one week, maximum effect at 6 weeks • No dependence, non-addicting

**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.*

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

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.[25] The opportunistic infections seen in brain cancer patients include Pneumocystic jirovecii pneumonia (PJP, formerly pneumocystic carinii pneumonia or PCP), and Candida mucositis and esophagitis.[22] The incidence of PJP may also be increased in patients receiving temozolomide therapy for malignant gliomas.[25] The rate of PJP in patients with brain tumours is estimated to be 1 to 6%.[22] 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.[25]

Prevention:

PJP: It may be prudent to consider prophylactic therapy against PJP in brain cancer patients receiving prolonged corticosteroid therapy.[25] 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.[25] For patients allergic to sulfa drugs or trimethoprim, aerosolized, dapsone or atovaquone are effective alternatives.[25]

Table 6. PJP prophylaxis doses.[25,45,46]

Trimethoprim-sulfamethoxazole	DS (sulfamethoxazole 800 mg + trimethoprim 160 mg) three times weekly or SS (sulfamethoxazole 400 mg + trimethoprim 80 mg) daily
dapsone	50 mg daily (G6PD test is recommended)
atovaquone	1500 mg daily with food
dapsone + pyrimethamine + leucovorin	Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg, once weekly

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*:
  - difficulty swallowing
  - feeling like food is getting stuck in the throat

Treatment: Table 7 describes treatments for infections associated with steroid use.

Table 7. Treatment of infections associated with steroid use.[25,46]

PJP	
trimethoprim-sulfamethoxazole	po: 2 DS tabs every 8 hours x 21 days IV: sulfamethoxazole 15-20 mg/kg and trimethoprim 5 mg/kg every 8 hours x 21 days *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* [46]
trimethoprim + dapsone	trimethoprim po 320 mg or 15 mg/kg three times daily + dapsone 100 mg daily x 21 days
atovaquone suspension	po 750 mg twice daily with food x 21 days
clindamycin + primaquine	clindamycin po 300-450 mg po every 6 hours OR IV 600 mg every 8 hours + primaquine 15 mg po daily x 21 days
pentamidine	4 mg/kg/day IV x 21 days
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 oral solution without food has better absorption 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.[12,25,45] 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.[47] 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.[48] 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.[48] 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.[49,50]

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 2020 ASCO Guidelines for treatment of venous thromboembolism states that initial anticoagulation may involve LMWH, UFH, fondaparinux, or rivaroxaban for cancer patients with established VTE(2020).[47] 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.[47] The 2020 NCCN guidelines for VTE treatment include unfractionated heparin (UFH), LMWH or fondaparinux for acute treatment upon diagnosis of VTE.[48] 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.[51] Long term anticoagulation is recommended for patients with malignant gliomas.[25]

Limited safety data exists for the use of DOAC's in patients with primary CNS malignancies. A retrospective comparative cohort study in patients with primary brain tumours was conducted, they found that the cumulative incidence of any ICH was 0% in patients receiving DOACs vs. 36.8% (95% confidence interval [CI], 22.3–51.3%) in those treated with LMWH, with a major ICH incidence of 18.2% (95% CI, 8.4–31.0). Therefore based on these observations they concluded that DOACs are not associated with an increased incidence of brain hemorrhage.[52]

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Table 8. LMWH dosing.[48,53-56]

Dalteparin	• 200 U/kg sc daily x 30 days, then 150 U/kg sc daily • 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
Enoxaparin	• 1 mg/kg sc every 12 hours OR 1.5 mg/kg once daily for 5 to 10 days followed by long-term anticoagulation for a total duration of 3 to 6 mos
Tinzaparin	• 175 U/kg sc daily • Tinzaparin should be avoided in patients over 70 years of age with renal insufficiency.

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 < 30 mL/min.[48]

Table 9. DOAC dosing

Apixaban	10mg BID for 7 days then 5mg Po BID
Rivaroxaban	15mg Po BID for first 21 days then 20mg daily
Edoxaban	Initial therapy with LMWH or UFH for at least 5 days then edoxaban 60mg or 30mg (in patients with Cockcroft-gault estimated Crcl 30-50ml/min or weight<60kg or concomitant potent pgp inhibitors Had a clinically significant increase in major bleeding (Hokusai trial)
Dabigatran	Initial therapy with LMWH or UFH for at least 5 days then dabigatran 150 mg PO BID If above regimens are not appropriate/available No clinical trials yet on cancer patients

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).[37] 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.[31]

Two large observational studies in the literature evaluated the correlation between systemic corticosteroids and cardiovascular disease.[57,58] The first study revealed an increased risk of cardiovascular or cerebrovascular events (OR 1.25; 95% CI 1.21, 1.29).[57] The second study revealed a higher risk of cardiovascular events (OR 2.56; 95% CI 2.18, 2.99).[58]

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 in patients with corticosteroid-induced lipodystrophy is recommended.[31]

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.[22] Optimizing patient nutrition by encouraging a diet containing adequate protein is recommended.[18]
- 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.[59] Testosterone may reduce dexamethasone induced myopathy[60,61]. 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
- Cataracts-usually bilateral and slowly progressing
- Striae
- Hiccups
    - physical measures to relieve hiccups should be attempted first, although the efficacy of these measures is only evidenced by case reports:[62]
        - 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:[62]
        - chlorpromazine: 25 mg three four 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

Table 10. Summary of Common complications of steroid therapy

• **Side effect of steroid therapy**				
Disease	**Symptoms**	**Prevention**	**Monitoring and Assessment**	**Treatment**
Endocrine Complications Hyperglycemia	• Polyuria, polydipsia, and polyphagia, Vulvovaginitis, • Urinary tract infections, surgical wound infections • Other Symptoms:	• Diet and exercise • Limited consumption of snacks, juices, milk and simple carbohydrate sources	• Glucose monitoring	• Measurement of glucose levels • Fasting glucose and daytime glucose levels

	• Increased thirst, frequent urination, headaches, difficulty concentrating, blurred vision, fatigue (weak, tired feeling), increased hunger, weight loss			
Muscular Complications Myopathy	• Muscle atrophy, muscle weakness and eventual wasting, especially of the pelvic girdle	• Lowest possible dose of dexamethasone • Exercise • Physiotherapy	• Difficulty climbing stairs • Patient cannot rise from a chair • Patient cannot ambulate independentl • Patient cannot lift extremities against gravity or complete bed mobility skills independently • Evaluation of neck and hip flexor strength, Estimates of overall endurance	• Switch the medication or lower dose of Dexamethasone • Switch to non-fluorinated corticosteroids (prednisone or hydrocortisone)
Skeletal Complications	• Hip pain especially upon weight-bearing; buttock, thigh or knee pain	• Regular active weight-bearing exercise • Calcium (diet and suppl) 1200 mg daily • Vitamin D 800 – 2000 IU daily • Fall prevention strategies	• Pain measurement and assessment	• Patients should refer to an endocrinologist or rheumatologist, and to an orthopedic surgeon for compression fractures.
Gastrointestinal (GI) Complications	• Gnawing or burning epigastric pain,nausea • Loss of appetite, bloating, feeling of fullness, vomiting • Melena or hematemesis/ • Severe abdominal pain	• Proton pump inhibitors and H2 blockers		• Rectal exam, • H. pylori test, • Proton pump inhibitors
Psychiatric Complications	• Anxiety • Irritability • Insomnia	• Corticosteroid dose, • Regular sleep/rest pattern, • Avoid smoking, alcohol and/or caffeinated drinks, meditation, • Avoid vigorous exercise before bedtime	• Screening tool to identify • Distress	• Psychological assessment • Cognitive behavioral therapy, • Intensive psychotherapy, and group therapy
Infections	• Symptoms of PJP: • Cough, fever, chest pain, increased respiratory rate, fatigue		• PJP: corticosteroid therapy	

	• Symptoms of Candida mucositis: • White slightly raised lesions on the tongue and inner cheeks, burning sensation in the mouth and throat, cracking of mouth, cottony feeling in mouth, loss of taste • Symptoms of Candida esophagitis • Difficulty swallowing, feeling like food is getting stuck in the throat			
Hematologic Complications	• Sudden onset of cough, Sharp chest pain • Rapid breathing or shortness of breath, Lightheadedness	• Routine prophylaxis with an antithrombotic agent is not recommended	• Swelling in one or both legs, • Pain or tenderness in one or both legs, • Red or discolored skin in the affected leg • Visible surface veins	• Dalteparin, • Enoxaparin • Tinzaparin
Cardiovascular Complications	• Increase in blood pressure			• Screening for corticosteroid-induced hypertension, particularly during the first months of therapy in patients with corticosteroid-induced lipodystrophy

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Development and Revision History

This guideline was reviewed and endorsed by the Alberta CNS Tumour Team. Members of the CNS Tumour Team include surgical oncologists, radiation oncologists, medical oncologists, neurologists, neurosurgeons, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta CNS Tumour Team, external participants identified by the Working Group Lead, and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2013 and updated in 2021.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2022. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

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

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial CNS Tumour Team and are a 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.

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