PM R 11 (2019) 409-419

www.pmrjournal.org

Narrative Review

Systemic Absorption and Side Effects of Locally Injected Glucocorticoids

Alison Stout, DO, Janna Friedly, MD, Christopher J. Standaert, MD

Abstract

Local glucocorticoid injections are often used to treat joint, soft tissue, or spinal pain, but the systemic side effects associated with these injections are poorly understood and not well recognized. There are significant known risks to systemic administration of glucocorticoids. However, there are no guidelines that address issues of systemic absorption, overall systemic risks, or other side effects of locally injected glucocorticoids. For this review, a literature search was performed, and the available evidence on systemic absorption and clinical side effects of intra-articular and epidural glucocorticoids was synthesized. The goal was to improve clinical understanding of risks associated with these injections. Existing data suggest there is significant individual variability in the amount of systemic absorption and clinical effects of locally injected glucocorticoids. However, it is clear that both intra-articular and epidural injections can have systemic effects for weeks and that complications may be associated with their use, including Cushing syndrome, loss of bone density, infection, and hyperglycemia. The concurrent use of oral steroids, the number of injections, and the type and dose of glucocorticoids used all are important considerations in estimating risks. The total dose calculation of cumulative glucocorticoid exposure should include all local injections. Caution should be exercised when local glucocorticoid injections are used in higher risk patients, such as postmenopausal women, people with diabetes, and those considering surgery in the near term. Better provider awareness of possible systemic risks should improve decision making and informed consent with patients when considering intra-articular and epidural steroid injections for painful conditions.
Level of Evidence: IV

Introduction

Corticosteroids are commonly used in clinical practice to decrease inflammation and have well-established side effects particularly with long-term oral administration of corticosteroids including the appearance of Cushingoid features, osteoporosis, and immunosuppression. However, the systemic absorption and side effects associated with local injection are often underappreciated. As local injections may be considered simply the administration of corticosteroid to a finite area, the systemic effects that can arise from a local injection may be underestimated. Understanding the absorption characteristics and systemic effects of local injections is important to determine the appropriate use of these drugs. The objective of this article is to describe the available evidence on systemic absorption and clinical effects of locally injected glucocorticoids in order to improve clinician recognition of their potential systemic risks. A PubMed/-MEDLINE literature search was conducted to include all articles published until December 2017. The key words that were used to identify articles of interest included the Boolean search string: "epidural steroid injections" OR "intra-articular steroid injection" in combination with any systemic absorption condition related to systemic steroid injections such as "bone mineral density," "vertebral fracture," "osteoporosis," "diabetes," "glucose," infection," "immunosuppression," "Cushingoid," "endocrine," "psychiatric," "cardiac," "myopathy," and "avascular necrosis." References of all articles were also reviewed for additional relevant studies. Articles were excluded if they were not published in English. From January 2018 through June 2018, all articles published through PubMed including "epidural steroid injection" in the key words were review for inclusion.

https://dx.doi.org/10.1002/pmrj.12042

General Systemic Effects

Most exogenously administered corticosteroids are predominantly glucocorticoids. Glucocorticoids affect the entire endocrine system, including glucose metabolism, bone metabolism, immune function, serum lipids, adiposity, the gastrointestinal system, mood and depression, sex hormones and the cardiovascular system. In the hypothalamic-pituitary-adrenal (HPA) axis, the primary effects of glucocorticoids are to decrease adrenocorticotropic hormone (ACTH) and serum cortisol. They also inhibit thyroid stimulating hormone (TSH), gonadotropins, testosterone, insulin-like growth factor 1 (IGF-1), transforming growth factor beta (TGF-B), and growth hormone.[1] Cortisol suppression after glucocorticoid administration is a marker of systemic absorption and alteration of the hypothalamic-pituitary-adrenal axis. Studies on orally administered glucocorticoids have shown that there is not predictable HPA axis suppression by dose or duration of treatment and that there is substantial individual variation in clinical effects.[2,3]

Bone mineralization is the most widely studied effect of systemic glucocorticoids (Figure 1). Glucocorticoids lead to an increase in osteoclast activity and urinary excretion of calcium while decreasing osteoblast activity and gastrointestinal absorption of calcium with the net effect of decreasing bone density.[4] The decrease in bone density from orally administered glucocorticoids has been well demonstrated even at dosages of prednisolone or equivalent (Table 1) as low as 2.5 to 7.5 mg daily.[5,6]

Increased susceptibility to infection is another known side effect of systemic glucocorticoids. Postsurgical infection has been noted to increase in patients who have received glucocorticoids within 30 days prior to surgery.[7] One retrospective cohort of 635 235 surgical patients demonstrated a twofold increase in wound infections with a slightly higher incidence of deep infections in those who were treated with glucocorticoids within 30 days prior to surgery compared to those who were not treated with glucocorticoids.[7] In addition, overall morbidity and death were higher in the glucocorticoid group than the patients without glucocorticoid use.

Other glucocorticoid systemic effects are also well established. Neuropsychiatric effects from systemically administered glucocorticoids include depression, bipolar/manic state, and psychosis.[8,9] Additionally, neuron loss and atrophy in the hippocampus are documented in stressed or glucocorticoid treated animals.[8,10] Chronic systemic glucocorticoids are also associated with multiple adverse effects on the cardiovascular system including hypertension, hypercholesterolemia, hypertriglyceridemia, endothelial damage, and hypercoagulability.[11] Other known effects from systemically administered glucocorticoids include hyperglycemia, avascular necrosis, sex hormone changes, Cushing syndrome, myopathy, and muscle wasting. Because of these known side effects, there have been long-standing efforts to minimize the use of long-term systemic glucocorticoids.[5] A direct comparison of HPA axis suppression after epidural steroid injection (ESI) or intra-articular injection compared to

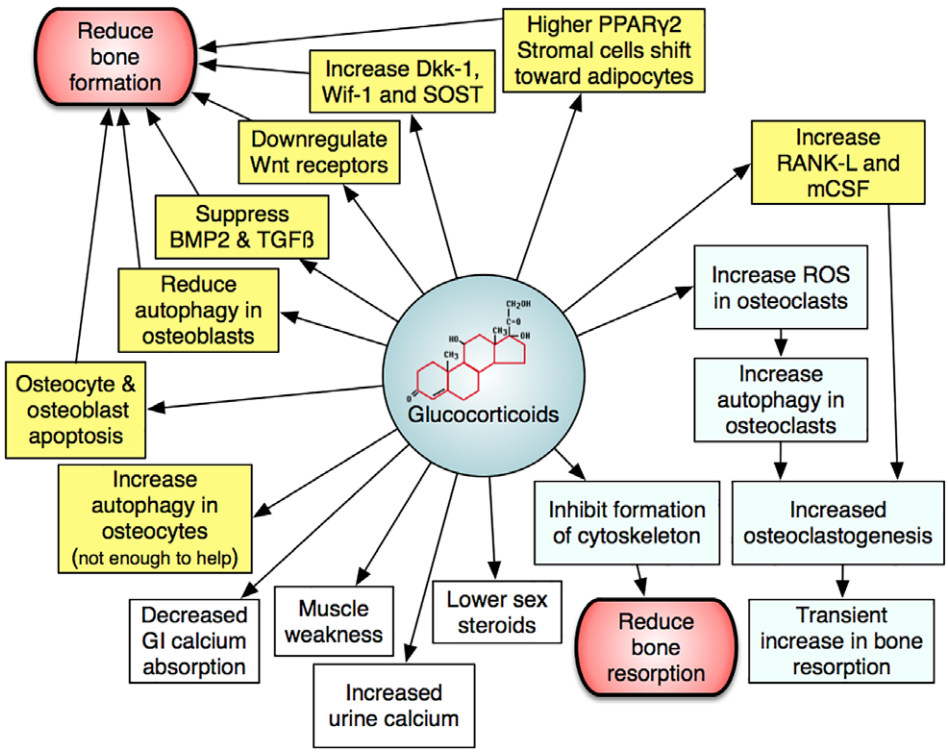

Figure 1. Glucocorticoid effects on bone metabolism (University of Washington©).

orally administered glucocorticoids has not yet been made.

Local Injection

Although the amount of systemic absorption and the side effects associated with local injections are not well understood, all of the effects associated with systemic use can also occur with locally injected glucocorticoids. This raises a number of clinical considerations for local injections, particularly because a given patient may often receive injections into multiple different sites by different providers in routine practice. Quantifying systemic dose and risk is challenging, beginning with the idea of identifying a maximum safe number of injections or total milligrams of glucocorticoid injected per year. Although there are wide variations in clinical practice, some publications have recommended the maximum dose of epidural glucocorticoid injections be limited to 3 mg/kg (triamcinolone equivalents [Table 1]) per year.[12] However, there is ambiguity in this recommendation, and posing this limit raises many more questions. For example, is it the total dose that is most important or are the effects related to the number of injections performed and the structures or regions injected? Can this maximum dose be safely repeated year after year indefinitely? How do we factor in ongoing peripheral injections in multiple sites and oral steroid therapy? Clinical recommendations on the frequency of injections varies, and many providers base their limits on coverage policies rather than on systemic effects of glucocorticoids. Payer coverage determinations are not necessarily based on risk of systemic effects, such as in Washington State where a maximum of three epidural injections (total in any body region) in 6 months are covered.[13] Providers may not understand the limitations of these coverage recommendations, and this speaks to the need for better understanding of the data on systemic effects and safety associated with these procedures.

Systemic Absorption

Intra-Articular Glucocorticoids

HPA axis suppression lasting for weeks after intra-articular injection has been documented since the early 1960s.[14] This prolonged suppression mirrors the duration of widespread decreases in generalized joint inflammation after a local intra-articular injection.[14,15] It has also been demonstrated that glucocorticoid is absorbed from the joint more slowly than the identical oral dose.[16] This absorption can lead to HPA axis suppression for several weeks after intra-articular injection. Cook noted detectable levels of triamcinolone in the serum with associated HPA axis suppression up to 4 weeks after a single intra-articular injection.[17] A recent review of HPA axis suppression after intra-articular glucocorticoid injection echoed similar findings with recovery to baseline depending on medication, dose, and frequency of injections.[18] In addition, the duration of HPA axis suppression after intra-articular glucocorticoid injection also has individual patient variability for which specific risk factors have not been identified.[18]

Regarding dose effects, one study of 21 patients with methylprednisolone 40 or 80 mg injected into one or both knees found that serum glucocorticoid levels were dependent on the number of joints injected, rather than on the total amount of glucocorticoid injected.[19] In this study by Armstrong et al, an injection of 40 mg methylprednisolone into each knee (80 mg total) resulted in greater serum glucocorticoid levels than 80 mg injected into a single knee. For doses of 40 mg or greater, all caused near complete cortisol suppression for several days, and in all but 3 of 21 participants, cortisol levels returned to within normal range after 1 week.[19] The authors concluded that the magnitude and duration of HPA axis suppression were not related to the systemic levels of prednisolone nor to the amount of glucocorticoid or number of joints injected (in doses ≥40 mg of methylprednisolone). Rather, any dose of 40 mg of methylprednisolone or more resulted in complete HPA suppression for up to 1 week.[19] Although just a single study, it is plausible that injection of multiple joints increases systemic glucocorticoid absorption, but that the amount of absorption from a single injection at current standard doses is enough to cause complete HPA axis suppression in most patients.

Epidural Glucocorticoids

In the 1970s, spinal injections with glucocorticoids were noted to have systemic absorption with potential HPA axis suppression. In 1974, a study of 72 patients receiving lumbar ESI with 80 to 120 mg methylprednisolone demonstrated that about 50% had cortisol levels below their baseline at 3 weeks post injection.[20] In dogs, an epidural dose of 2 mg/kg of triamcinolone resulted in failure of cortisol response to insulin-induced hypoglycemia for 4 weeks, returning to normal at 5 weeks post injection.[21]

In order to determine the amount and duration of adrenal suppression with "standard" doses of epidural steroids, Kay and colleagues prospectively studied 14 patients receiving three nonfluoroscopically guided ESIs with 80 mg of triamcinolone at weekly intervals with or without midazolam for sedation. Mean cortisol and ACTH levels were decreased at 1 month after the last ESI, but this was statistically significant only in those who had received midazolam. Cortisol and ACTH were not measured beyond 1 month after the last ESI. Cortisol response to ACTH challenge was measured preinjection and at 1 and 3 months after the last ESI. Five of 14 patients had an abnormal response at the 1-month follow-up (three had received midazolam and two had not). At 3 months, a normal response was obtained in all patients. The authors recommended that patients who have had ESIs within the previous 3 months have supplemental glucocorticoid therapy for surgical stress as their adrenal system may still be unable to respond appropriately.[22] The authors did not

discuss the potential of other deleterious systemic effects and it is unknown whether any of these patients had symptoms relevant to HPA axis suppression.

A report from 2003 measured cortisol measured cortisol levels in two nondiabetic, glucocorticoid naïve individuals after a single ESI with 160 mg of methylprednisolone.[23] In these two patients, there was complete adrenal suppression for 6 days and incomplete suppression for at least 4 weeks with detectable levels of serum methylprednisolone also present during this period. It is unknown when cortisol levels returned to normal or when serum methylprednisolone became undetectable. Although the technical details of the procedures were not included, which may have introduced confounders, these findings are consistent with the prior studies.

A recent study measuring serum triamcinolone levels of eight patients undergoing fluoroscopically guided cervical interlaminar ESIs injected with 80 mg triamcinolone showed a median terminal elimination half-life of 219 hours (range 121-681).[24] They noted that the median elimination half-life after lumbar ESI in their earlier study was much longer (523 hours).[25] The small number of participants in each study limits conclusions, but ESI systemic absorption may vary between spinal regions.

Recently, a randomized trial of 400 patients aged 50 years and older receiving epidural injections with either local anesthetic only or local anesthetic plus glucocorticoid demonstrated that 20.3% of those given glucocorticoid (dexamethasone, betamethasone, methylprednisolone, or triamcinolone) had >50% cortisol reduction at 3 weeks compared to 6.7% in the lidocaine alone group.[26] In this study, no baseline patient or procedural characteristics were associated with the degree of cortisol suppression with the exception of the type of glucocorticoid administered. Those receiving methylprednisolone or triamcinolone were more affected and had an average cortisol reduction of 41% at 3 weeks. Time to normalization of cortisol was not able to be determined by the data. There was an unclear association between cortisol suppression and patient self-reported adverse events, so the clinical impact of this cortisol suppression is still unknown. However, in this study, one patient with underlying chronic obstructive pulmonary disease on inhaled glucocorticoids with nearly complete cortisol suppression up to 3 weeks developed pneumonia that required hospitalization 1 week after the epidural injection. Overall, the available evidence suggests that there is significant systemic absorption of glucocorticoid after ESI. However, the effect on HPA axis suppression is variable and there is only one large prospective study that addresses this issue.

Solubility of Glucocorticoids

Systemic absorption and availability may differ based on the solubility of glucocorticoids. For intra-articular injections, the duration of local and systemic effect is greater for less soluble glucocorticoids as demonstrated in patients after a single knee injection with different formulations of prednisolone.[27] In contrast to some of the studies discussed previously, a cohort study of 20 patients receiving a single knee injection with 6 mg of betamethasone (dose equivalent to triamcinolone 40 mg [Table 1]), which is more soluble than triamcinolone and methylprednisolone, did not demonstrate HPA-axis suppression.[28]

There has been some investigation of HPA axis suppression based on glucocorticoid solubility in ESIs as well. In the large clinical trial on ESIs noted above, Friedly et al demonstrated that after dexamethasone or betamethasone injection, cortisol suppression was comparable to the lidocaine only arm.[26] However, one cohort study of nine patients following a single ESI with 15 mg of dexamethasone describes profound HPA axis suppression at 7 days with normal cortisol levels at 3 weeks.[29] Therefore, current evidence suggests that more soluble glucocorticoids have a shorter duration of systemic effect than is associated with less soluble glucocorticoids.

Drug-Drug Interactions

The case reports of severe and prolonged systemic effects of spinal glucocorticoids raise concern about predisposing individual factors. Medication interactions is one primary suspect. There have been several studies on the potent cytochrome P450 3A4 inhibitor ritonavir in combination with glucocorticoids. Several case reports demonstrate that a single intra-articular injection can result in iatrogenic Cushing's and adrenal failure with adrenal suppression lasting up to 8 months[30] and case reports of Cushing's after ESI have also been published.[31,32] In patients with HIV on ritonavir, even inhaled glucocorticoids have caused iatrogenic Cushing's and secondary adrenal insufficiency.[33] Ritonavir is one of the most potent inhibitors of the P450 3A4 pathway, and as glucocorticoids are metabolized by the same cytochrome pathway, ritonavir administration can significantly decrease or block the clearance of glucocorticoids.

Other medications also inhibit the P450 3A4 pathway and could also lead to decreased clearance of glucocorticoids (Table 2).[34,35] The vast number of medications involved in the pathway precludes individualized discussion of all of them. However, midazolam, often given during spinal injections, could further predispose patients to systemic effects of spinal glucocorticoids due to this cytochrome inhibition. It is both a substrate and a competitive inhibitor of the P450 3A4 pathway and has been shown to decrease fentanyl degradation in the liver.[34] This theory is supported by the study of Kay et al[22] showing that ACTH suppression after ESI was greater if participants had received preinjection midazolam.

Clinical Effects

Cushing Syndrome

Cushing syndrome arises from excessive production of cortisol and is associated with a number of physiological

Table 1
Commonly injected glucocorticoids dose equivalent

Glucocorticoid	Approximate equivalent dose (mg)
Triamcinolone	4
Methylprednisolone	4
Dexamethasone	0.75
Betamethasone	0.6-0.75

changes including facial and trunk obesity, hypertension, stretch marks, weakness, facial hair growth in females, and osteoporosis. Exogenous Cushing syndrome can occur from locally injected glucocorticoids. Multiple intra-articular glucocorticoid injections performed over time can have clinically significant endocrine effects. As an example, one case was reported of a 49-year-old woman initially thought to have a pituitary cause of growth hormone deficiency.[36] She had Cushingoid features but decreased ACTH and cortisol. Further testing revealed triamcinolone in her urine. She recalled having several injections but reported being unaware that they contained glucocorticoids. She had been injected with a total of 510 mg of triamcinolone and 40 mg of methylprednisolone into the vertebral and costochondral joints over 28 months. Nine months after her last injection, urine triamcinolone was still detectable.

Case reports of exogenous Cushing syndrome after epidural and other spine injections began to emerge in the 1990s. One case report described Cushing syndrome after a single ESI with HPA axis suppression lasting 6 months[37] and another lasting 8 months.[38] In a case series, Edmonds et al described prolonged cortisol suppression and symptomatic Cushingoid features in three patients after receiving (1) a single set of zygapophysial injections (150 mg triamcinolone over four lumbar joints); (2) a series of two interspinous ligament injections 1 month apart (150 mg triamcinolone with each); and (3) a series of eight cervical paraspinal steroid injections followed by a single epidural injection over 3 months (total dose of 286 mg methylprednisolone).[39] The authors postulated that to avoid these side effects, the minimum number of locations with the minimum amount of steroid should be used. They also recommended that injections be performed more than 6 weeks apart and to consider perioperative stress dose glucocorticoids in patients undergoing surgery after recent spinal steroid injections. However, these recommendations were based on their small case series with no prospective data.

Case reports of symptomatic exogenous Cushing syndrome specifically after ESIs have been published as well.[36] A 54-year-old woman who had had 15 ESIs (up to 40 mg of triamcinolone each) over 3 years did not present with any Cushingoid features but had severe weakness and loss of appetite. She was found to have decreased ACTH, cortisol, and IGF-1 levels. Sixty-two days after her last ESI, she still had triamcinolone in her urine and decreased cortisol, finally returning to normal at 9 months. In this case report, the lag time to diagnosis was partially attributed to the underappreciation of the systemic effects of injected glucocorticoids by the physicians performing the injections and the resultant lack of information given to the patient.[20] Another case demonstrated Cushingoid features in a 53-year-old woman with "borderline diabetes" who had three caudal ESIs with 80 mg of triamcinolone each over 4 months. It took 6 months for adrenal function to return to normal.[40]

Table 2
Familiar cytochrome P450 3A4 drugs with potential to interact with glucocorticoids (does not represent a complete list)

CYP3A4 substrates	CYP3A4 inhibitors
ANTIHISTAMINES: Astemizole, chlorpheniramine **ANTIEMETIC:** Ondansetron **ANESTHESIA/PAIN:** Fentanyl, lidocaine, methadone **ANTIBIOTIC/ANTIVIRAL:** Clarithromycin, efavirenz, erythromycin (not CYP3A5), protease inhibitors, nevirapine, quinine **CARDIOVASCULAR:** Amlodipine, diltiazem, eplerenone, nifedipine, propranolol, quinidine, verapamil **HMG COA REDUCTASE INHIBITORS:** Atorvastatin, lovastatin **IMMUNE MODULATORS:** Cyclosporine, tacrolimus **NEUROPSYCHIATRIC:** Alprazolam, diazepam, midazolam, haloperidol, aripiprazole, buspirone, carbamazepine, pimozide, quetiapine, risperidone, trazadone, zaleplon, ziprasidone, zolpidem **ONCOLOGY:** Docetaxel, imatinib mesylate (Gleevec), irinotecan, paclitaxel, romidepsin, sorafenib, sunitinib, temsirolimus (Torisel), vemurafenib, vincristine **PULMONARY:** Salmeterol, sildenafil **STEROID:** Dexamethasone, estradiol, hydrocortisone, progesterone, testosterone **OTHER:** Cocaine, dapsone, dextromethorphan, finasteride, nateglinide	**STRONG INHIBITORS:** Clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, ritonavir, saquinavir, buprenorphine/naloxone (Suboxone) **INTERMEDIATE INHIBITORS:** Aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil, diltiazem **WEAK INHIBITORS:** Cimetidine **OTHER POSSIBLE INHIBITORS:** Amiodarone, chloramphenicol, ciprofloxacin, delavirdine, fluvoxamine, other protease inhibitors, norfloxacin, norfluoxetine, starfruit, voriconazole

Glucose Metabolism

Hyperglycemia after intra-articular injection or ESI has been demonstrated in patients with and without diabetes. For nondiabetic patients, a study of patients receiving ESI or glenohumeral joint injection, serum glucose was elevated for approximately 1 day.[41] Another study of 10 healthy volunteers receiving a single caudal ESI with 80 mg of triamcinolone demonstrated significantly increased fasting insulin and glucose with decreased glucose clearance at 24 hours, returning to normal at 1 week.[42] It should be noted that the authors embarked on this study after a 65-year-old patient with diabetes mellitus with a hemoglobin A1c of 7.5 developed hyperosmolar nonketotic hyperglycemic coma 24 hours after a single ESI with 80 mg of triamcinolone. This single published case report demonstrates that profound hyperglycemia after a single ESI is possible in diabetic patients.

Two studies on diabetic patients have demonstrated serum glucose elevations on average of 106 mg/dL and 126 mg/dL for 2 and 3 days respectively after a single ESI.[43,44] In a study of 18 patients receiving ESIs and 11 patients receiving a glenohumeral injection, serum glucose remained elevated for 7 to 14 days in diabetic patients.[41] The authors of this study could not determine if ESI or intra-articular injection caused more significant hyperglycemia.

Diabetic patients may have additional risk of systemic effects from locally injected glucocorticoids because of significantly reduced cytochrome p450 3A4 expression and activity.[45] This would further decrease clearance of glucocorticoids in this population, thereby increasing the duration of systemic side effects.

Bone Metabolism

Given the known effects of glucocorticoids on bone density, there is concern for deleterious changes from local injections. However, there are no studies that establish the extent of systemic bone demineralization after intra-articular glucocorticoid injections. For intra-articular glucocorticoid injection, it has been shown that serum osteocalcin is markedly decreased at 1 day but normal at 14 days.[46] For ESIs, Kerezoudis et al recently reviewed eight studies that assessed the effect of ESI on bone mineral density (BMD) and vertebral fracture risk.[47] They noted that four out of six studies on BMD found that ESIs were associated with decreased BMD and that one out of two relevant studies demonstrated increased vertebral fracture risk. An additional study published since the time of that review also suggests that ESIs are associated with decreased BMD in a dose-dependent fashion in postmenopausal women in South Korea.[48]

The negative effect of ESIs on BMD has been most studied in postmenopausal women. A single ESI with 80 mg of triamcinolone can decrease BMD of the hip in this population.[49] Kim et al also identified decreased BMD in a group of postmenopausal women undergoing multiple ESIs over an average of 34.4 months with cumulative mean dose of 400 mg.[50] A study from the same center found that serial ESIs using less than a total of 200 mg of triamcinolone in postmenopausal women over 1 year did not significantly affect BMD, but that doses over 200 mg per year should be avoided.[51] These findings together suggest that less than 200 mg within 1 year may be safe in postmenopausal women, but continuing this practice over successive years increases BMD loss. However, a separate study of 126 postmenopausal women receiving a mean of 3.6 ESIs with mean cumulative dose of 9 mg dexamethasone (48 mg triamcinolone equivalent [Table 1]) demonstrated decreased BMD except in those taking antiosteoporotic medications (excluding calcium and vitamin D).[52] This suggests that doses of epidural steroid less than 200 mg triamcinolone equivalents could result in decreased BMD. They went on to recommend prophylactic antiosteoporotic treatment be considered in postmenopausal women receiving ESIs.

For vertebral fracture, a large retrospective cohort study of 3415 patients demonstrated that ESIs increase the likelihood of vertebral fracture (relative risk of 1.21) for each successive injection.[53] In contrast, a retrospective cohort study by Yi et al concluded that ESIs were not associated with fractures or low BMD.[54] This study examined 352 postmenopausal women who received ESIs and divided them into those who sustained a fracture and those who did not. They found that the fracture group had significantly higher age, lower BMD, and weight and felt that this accounted for the higher risk of fracture. However, they evaluated only mean data and did not control for the number of injections or dose of steroid. They also found the prevalence rate of vertebral fractures was 22% in their population of Korean women undergoing a mean of 4.1 ESIs, which is quite similar to the 20.9% prevalence rate for vertebral fractures that they cite for Korean women with glucocorticoid induced osteoporosis.[55] Given this, their data could suggest that, in Korean women, multiple ESIs may be associated with a vertebral fracture rate similar to that occurring in those with glucocorticoid induced osteoporosis and that postmenopausal women who already have a higher risk for fracture may be more affected.

The two studies discussed in the review of Kerezoudis et al[47] that did not find decreased BMD associated with ESIs both had significant methodologic limitations. One of these was a small study in which the rates of osteopenia and osteoporosis were much higher than seen in the general population.[23] The other study included 204 patients and found no change in BMD after standard doses of spinal steroids.[56] However, this study included a range of injections (including some in which steroids are not typically used), had insufficient data on concurrent treatments for osteoporosis, and assessed BMD at the forearm, which has questionable validity. Overall, the predominance of evidence supports the idea that

epidural steroids have deleterious effects on BMD and may increase the risk of vertebral fracture, particularly in postmenopausal women. Additional data are needed to fully understand the effects on BMD in premenopausal women and in men; however, the studies that have included these populations suggest similar concerns with decreased BMD.[53,57]

Immunosuppression

Immunosuppression does seem to occur after local or epidural injection of steroids. There have been two case reports documenting herpes zoster flares remote from the site of ESI but immediately following ESI.[58,59] In two other cases, devastating avascular retinal necrosis due to the reactivation of herpes zoster following ESI has been cited.[60] These patients had permanent visual changes despite treatment. These cases suggest that ESI causes decreased efficacy of the immune system; however, the extent of this effect is largely unknown.

Systemic and locally injected steroids have been directly implicated in infection after joint replacement. A study of infection rates after hip or knee arthroplasty found a twofold increase in the risk of prosthetic infection in those that received systemic glucocorticoids for more than 1 week within 1 year prior to surgery.[61] Kaspar et al examined infection rates in 40 patients undergoing hip arthroplasty who had received prior intra-articular steroid injection compared to 40 who did not previously receive injections.[62] Ten percent who had received prior steroid injections developed postarthroplasty deep infection compared to none in the control group.[62] A review of 144 patients who had undergone total hip arthroplasty identified deep infections in three patients, all of whom had prior intra-articular steroid injections.[63] The largest database study of patients undergoing total hip arthroplasty on 173 958 participants found a 40% increase in risk for postoperative periprosthetic infection in those injected within 3 months prior to surgery.[64] In a separate matched cohort study, 106 patients who had more than two glucocorticoid injections in the 12 months prior to total hip arthroplasty showed a threefold risk of postoperative infection (6.6%) compared to a matched group of 350 patients who received a single hip injection in the year before hip replacement (2.0%).[65]

The risk of postoperative infection associated with ESI, from either systemic or local effects, has recently been studied, as well. In 18 931 patients aged 65 years old and older who underwent a single-level lumbar decompression surgery within 1 year of ESI, the incidence of postoperative infection was significantly greater in those receiving an ESI within 1 to 3 months prior to surgery (1 month OR = 3.2, 1 to 3 months OR = 1.3).[66] A study of 847 patients in the military health system who received ESI within 90 days of surgery demonstrated an increased odds ratio of 1.57 for injected patients compared to controls.[67] A study of surgery with or without the use of epidural steroid paste to control pain during lumbar decompression surgery in 283 patients documented that there was an increased incidence of infections in the patients receiving paste compared to the nonpaste group (odds ratio 6.4).[68] The risk of postoperative infection in lumbar fusion after preoperative ESI has also been retrospectively evaluated in 88 540 patients.[69] It demonstrated that lumbar ESI within 3 months of lumbar fusion is associated with an increased rate of postoperative infection. The combined data supports the idea that ESI within 3 months of lumbar decompression or fusion surgery may increase postoperative infection risk, especially in patients over 65 years of age. When considered with the data on the effect of ESI on BMD, ESI could theoretically pose an additional risk of nonunion in patients undergoing fusion after ESI, but this has not been clinically evaluated.

Neuropsychiatric Changes

Injected glucocorticoids can lead to temporary mania and psychosis in some patients. There are multiple case reports but no known incidence or dose correlation.[70-73] Some of these cases involve patients with preexisting psychiatric conditions, but many do not.

Patients with major depression also show resistance to glucocorticoid at target tissues.[74] It is also notable that stress actually increases functional resistance to glucocorticoids in the absence of increased cortisol.[8] Given this resistance, it is possible that patients with major depression or extreme stress could have less benefit from local glucocorticoid injection. This would seem to correlate with data suggesting worse outcomes for ESI in those with depressed affect[75]; however, this relationship has not been directly studied.

Other Clinical Effects

There are various other systemic clinical effects that are even less understood. Osteonecrosis of the femoral head and glenohumeral joints has been documented after intra-articular glucocorticoid injection.[76] However, osteonecrosis of the femoral head after ESI has not been reported in the scientific literature.

Sex hormones are affected by glucocorticoid injection. Glucocorticoids given intra-articularly are known to decrease estrogen and androgens. In one study of 18 women with rheumatoid arthritis, sex hormones were monitored for 2 weeks following intra-articular injection of 20 mg triamcinolone. At 2 weeks post injection, both estrogen and androgen levels were decreased but were returning toward baseline, though testosterone levels remained significantly decreased from baseline levels. In this study, participants were followed for only 2 weeks; therefore, the total duration of testosterone suppression is unknown.[77] Sex hormone levels after ESI have not been measured. Although physicians have noted patient

complaints of menstrual abnormalities after ESI, dysfunctional uterine bleeding after ESI has been described in only one case report.[78]

Short-term cardiovascular changes are likely due to locally injected glucocorticoids. Increased blood pressure does occur after ESI.[41] It is not known if other effects such as hypercoagulability also occur.

Additional clinical effects have also been published in case reports including symptomatic epidural lipomatosis,[79-81] steroid myopathy after a single ESI,[82] and subcapsular cataracts after multiple ESIs.[83]

Discussion

The local injection of steroids is clearly associated with a number of systemic effects that are inadequately studied and underappreciated. Although the evidence regarding the systemic effects of local glucocorticoid injections is variable, there is sufficient direct and indirect evidence that can reasonably be applied in order to develop preventative strategies until further direct evidence is published.

Guidelines regarding the maximum dose of locally injected glucocorticoid administered per year have yet to be clearly established. It is clear that both intra-articular and epidural injections can cause several weeks of systemic effect, and the total dose calculation should include all local injections. The concurrent use of oral steroids, the number of injections, the steroids used, and the timing of any major surgical procedures may all be important considerations.

From available data on systemic absorption and BMD loss, providers should consider that local glucocorticoid injection could result in loss of BMD, especially in susceptible populations such as postmenopausal women or those already with osteoporosis. Given the available evidence, postmenopausal women and potentially men over age 50, a maximum cumulative whole body triamcinolone/-methylprednisolone dose of 200 mg per year and 400 mg per 3 years should be considered. These relative limits, however, should be weighed against functional benefits. In those with osteoporosis, and especially in those already with a fragility fracture, treatment with bisphosphonates could be considered if receiving multiple injections. At a minimum, providers should discuss the potential of BMD loss after glucocorticoid injections with patients, especially when receiving multiple injections.

Authors have advocated to refrain from using ESI within 4 weeks of planned surgery because of the suppression of stress response.[39] Based on the available literature on large populations and glucocorticoid injection and postoperative infection, patients should be counseled that local glucocorticoid injection within 1 to 3 months prior to surgery may increase the risk of postoperative infection, especially in older patients or those with comorbidities. In addition, patients with underlying chronic conditions that predispose them to the development of infection (such as chronic obstructive pulmonary disease) and those who chronically use oral, inhaled, or intranasal glucocorticoids, may be at higher risk of developing infection related to ESI.

For patients with diabetes, it is difficult to ascertain a day of injection serum glucose or recent hemoglobin A1-c "cutoff" or limit for the safe administration of glucocorticoids. Nonetheless, patients with chronic inflammation have decreased response to the anti-inflammatory effect of glucocorticoids at target tissues and patients with diabetes have significantly reduced cytochrome p450 3A4 expression and activity.[8,45] These factors, combined with the isolated case of hyperglycemic coma in a patient with noninsulin dependent diabetes and a Hgb A1c of 7.5,[42] suggest that patients with poorly controlled diabetes have a less desirable risk-to-benefit ratio for glucocorticoid injection. Some institutions use a fasting glucose cutoff of 200 to 250 for ESI and intra-articular injection in most cases. There are no absolute cutoffs to prevent complication, but physicians should take into consideration the ability of the patient to monitor and manage their serum glucose levels after injection.

Understanding that locally injected glucocorticoid may also affect the central nervous system, mood, sex hormones, muscle tissue, and the cardiovascular system is key to fully understanding the risks incurred with repeated glucocorticoid injections. The systemic side effects of glucocorticoids injected for pain are mostly overlooked by the providers who perform these injections. Given the wide range of potential symptoms of HPA axis suppression, providers must consider the side effects of locally injected glucocorticoids when otherwise unexplained systemic symptoms present in patients.

All patients undergoing glucocorticoid injection should have a review of their medications, including recent glucocorticoid injections in other locations, for possible interactions. Patients on ritonavir should not be administered glucocorticoids. Further, the practice of sedation with midazolam during ESI should be reserved for patients with significant procedure-related anxiety and/or the need for relaxation in order to safely perform the procedure and discouraged in those at high risk of clinical side effects from glucocorticoids, such as those with osteoporosis. The use of concomitant oral, inhaled, intranasal, and even topical glucocorticoids could also potentiate systemic side effects and providers should take an inventory of other forms of glucocorticoids that patients may be using. Studies also suggest that injection of more soluble glucocorticoids may have a shorter duration of systemic effects.[26-29]

Conclusion

Although the data are varied, the general recommendation is that the total glucocorticoid dose should by considered and caution employed when using glucocorticoid injections, especially for postmenopausal women, people

with diabetes, and people considering surgery in the near future. Each patient's individual comorbidities and total glucocorticoid exposures need to be evaluated when considering the risk versus benefit of performing local glucocorticoid injections. Physicians may also need to include potential systemic effects in the differential diagnosis when addressing any postinjection symptoms in patients. All patients receiving glucocorticoid injections should be clearly educated about the potential systemic effects and counseled that these effects are variable between individuals during the process of informed consent and shared decision making.

References

1. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev.* 2000;21:55-89.
2. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol*. 2013;9:30.
3. Wilson AM, McFarlane LC, Lipworth BJ. Systemic bioactivity profiles of oral prednisolone and nebulized budesonide in adult asthmatics. *Chest*. 1998;114:1022-1027.
4. Marcus R, Feldman D, Kelsey J, eds. *Osteoporosis*. New York: Academic Press; 1996.
5. Grossman JM, Gordon R, Ranganath VK, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Care Res*. 2010;62:1515-1526.
6. Van Staa TPLH, Abenhaim L, Zhang B, Cooper C. Oral glucocorticoids and fracture risk: relationship to daily and cumulative doses. *Rheumatology (Oxford)*. 2000;39:1383-1389.
7. Ismael H, Horst M, Farooq M, Jordon J, Patton JH, Rubinfeld IS. Adverse effects of preoperative steroid use on surgical outcomes. *Am J Surg*. 2011;201:305-308; discussion 8-9.
8. Zunszain PA, Anacker C, Cattaneo A, Carvalho LA, Pariante CM. Glucocorticoids, cytokines and brain abnormalities in depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011;35:722-729.
9. Wada K, Yamada N, Sato T, et al. Corticosteroid-induced psychotic and mood disorders: diagnosis defined by DSM-IV and clinical pictures. *Psychosomatics*. 2001;42:461-466.
10. McEwen BS. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. *Metabolism*. 2005;54:20-23.
11. Maxwell SR, Moots RJ, Kendall MJ. Corticosteroids: do they damage the cardiovascular system? *Postgrad Med J*. 1994;70:863-870.
12. Deer TRM, Kapural L, Diwan SA. Guidelines for the proper use of epidural steroid injections for the chronic pain patient. *Tech Reg Anesth Pain Manag*. 2009;13:288-295.
13. WA State Health Technology Coverage Committee. *Spinal Injections*. 2016. http://www.hta.hca.wa.gov/documents/findings_decision_spinal_injections_061711.pdf. Accessed December 26, 2017.
14. Shuster S. Adrenal response to glucocorticoid treatment. *Lancet*. 2000;355:1458-1459; author reply 9.
15. Koehler BE, Urowitz MB, Killinger DW. The systemic effects of intra-articular corticosteroid. *J Rheumatol*. 1974;1:117-125.
16. Reeback JS, Chakraborty J, English J, Gibson T, Marks V. Plasma steroid levels after intra-articular injection of prednisolone acetate in patients with rheumatoid arthritis. *Ann Rheum Dis*. 1980;39:22-24.
17. Cook DM, Meikle AW, Bowman R. Systemic absorption of triamcinolone after a single intraarticular injection suppresses the pituitary–adrenal axis [abstract]. *Clin Res*. 1988;36:121A.
18. Johnston PC, Lansang MC, Chatterjee S, Kennedy L. Intra-articular glucocorticoid injections and their effect on hypothalamic-pituitary-adrenal (HPA)-axis function. *Endocrine*. 2015;48:410-416.
19. Armstrong RD, English J, Gibson T, Chakraborty J, Marks V. Serum methylprednisolone levels following intra-articular injection of methylprednisolone acetate. *Ann Rheum Dis*. 1981;40:571-574.
20. Burn JM, Langdon L. Duration of action of epidural methyl prednisolone. A study in patients with the lumbosciatic syndrome. *Am J Phys Med*. 1974;53:29-34.
21. Gorski DW, Rao TL, Glisson SN, Chinthagada M, El-Etr AA. Epidural triamcinolone and adrenal response to hypoglycemic stress in dogs. *Anesthesiology.* 1982;57:364-366.
22. Kay J, Findling JW, Raff H. Epidural triamcinolone suppresses the pituitary-adrenal axis in human subjects. *Anesth Analg*. 1994;79:501-505.
23. Dubois EF, Wagemans MF, Verdouw BC, et al. Lack of relationships between cumulative methylprednisolone dose and bone mineral density in healthy men and postmenopausal women with chronic low back pain. *Clin Rheumatol*. 2003;22:12-17.
24. Lamer TJ, Dickson RR, Gazelka HM, et al. Serum triamcinolone levels following cervical interlaminar epidural injection. *Pain Res Manag*. 2018;2018:8474127.
25. Hooten WM, Nicholson WT, Gazelka HM, Reid JM, Moeschler SM, Lamer TJ. Serum triamcinolone levels following interlaminar epidural injection. *Reg Anesth Pain Med*. 2016;41:75-79.
26. Friedly JL, Comstock BA, Heagerty PJ, et al. Systemic effects of epidural steroid injections for spinal stenosis. *Pain*. 2018;159:876-883.
27. Esselinckx W, Bacon PA, Ring EF, Crooke D, Collins AJ, Demottaz D. A thermographic assessment of three intra-articular prednisolone analogues given in rheumatoid synovitis. *Br J Clin Pharmacol*. 1978;5:447-451.
28. Habib G, Artul S, Chernin M, Hakim G, Jabbour A. The effect of intra-articular injection of betamethasone acetate/betamethasone sodium phosphate at the knee joint on the hypothalamic-pituitary-adrenal axis: a case-controlled study. *J Invest Med*. 2013;61:1104-1107.
29. Maillefert JF, Aho S, Huguenin MC, et al. Systemic effects of epidural dexamethasone injections. *Rev Rhum Engl Ed*. 1995;62:429-432.
30. Yombi JC, Maiter D, Belkhir L, Nzeusseu A, Vandercam B. Iatrogenic Cushing's syndrome and secondary adrenal insufficiency after a single intra-articular administration of triamcinolone acetonide in HIV-infected patients treated with ritonavir. *Clin Rheumatol*. 2008;27 (suppl 2):S79-S82.
31. Grierson MJ, Harrast MA. Iatrogenic Cushing syndrome after epidural steroid injections for lumbar radiculopathy in an HIV-infected patient treated with ritonavir: a case report highlighting drug interactions for spine interventionalists. *PM R*. 2012;4:234-237.
32. Ramanathan R, Pau AK, Busse KH, et al. Iatrogenic Cushing syndrome after epidural triamcinolone injections in an HIV type 1-infected patient receiving therapy with ritonavir-lopinavir. *Clin Infect Dis*. 2008;47:e97-e99.
33. Samaras K, Pett S, Gowers A, McMurchie M, Cooper DA. Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in human immunodeficiency virus-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: six cases. *J Clin Endocrinol Metab*. 2005;90:4394-4398.
34. Zhou SF, Xue CC, Yu XQ, Li C, Wang G. Clinically important drug interactions potentially involving mechanism-based inhibition of cytochrome P450 3A4 and the role of therapeutic drug monitoring. *Ther Drug Monit*. 2007;29:687-710.
35. Mayo Clinic. 2014. https://www.mayomedicallaboratories.com/it-mmfiles/Cytochrome_P450_3A4_and_3A5_Known_Drug_Interaction_Chart.pdf. Accessed July 7, 2018.
36. Lansang MC, Farmer T, Kennedy L. Diagnosing the unrecognized systemic absorption of intra-articular and epidural steroid injections. *Endocr Pract*. 2009;15:225-228.
37. Tuel SM, Meythaler JM, Cross LL. Cushing's syndrome from epidural methylprednisolone. *Pain*. 1990;40:81-84.
38. Horani MH, Silverberg AB. Secondary Cushing's syndrome after a single epidural injection of a corticosteroid. *Endocr Pract*. 2005;11:408-410.

39. Edmonds LC, Vance ML, Hughes JM. Morbidity from paraspinal depo corticosteroid injections for analgesia: Cushing's syndrome and adrenal suppression. *Anesth Analg*. 1991;72:820-822.
40. Leary J, Swislocki A. Hypothalamic-pituitary-adrenal suppression and iatrogenic Cushing's syndrome as a complication of epidural steroid injections. *Case Rep Endocrinol*. 2013;2013:617042.
41. Younes M, Neffati F, Touzi M, et al. Systemic effects of epidural and intra-articular glucocorticoid injections in diabetic and non-diabetic patients. *Joint Bone Spine*. 2007;74:472-476.
42. Ward A, Watson J, Wood P, Dunne C, Kerr D. Glucocorticoid epidural for sciatica: metabolic and endocrine sequelae. *Rheumatology (Oxford)*. 2002;41:68-71.
43. Gonzalez P, Laker SR, Sullivan W, Harwood JE, Akuthota V. The effects of epidural betamethasone on blood glucose in patients with diabetes mellitus. *PM R*. 2009;1:340-345.
44. Even JL, Crosby CG, Song Y, McGirt MJ, Devin CJ. Effects of epidural steroid injections on blood glucose levels in patients with diabetes mellitus. *Spine*. 2012;37:E46-E50.
45. Dostalek M, Court MH, Yan B, Akhlaghi F. Significantly reduced cytochrome P450 3A4 expression and activity in liver from humans with diabetes mellitus. *Br J Pharmacol*. 2011;163:937-947.
46. Emkey RD, Lindsay R, Lyssy J, Weisberg JS, Dempster DW, Shen V. The systemic effect of intraarticular administration of corticosteroid on markers of bone formation and bone resorption in patients with rheumatoid arthritis. *Arthritis Rheum*. 1996;39:277-282.
47. Kerezoudis P, Rinaldo L, Alvi MA, et al. The effect of epidural steroid injections on bone mineral density and vertebral fracture risk: a systematic review and critical appraisal of current literature. *Pain Med*. 2018;19:569-579.
48. Nah SY, Lee JH, Lee JH. Effects of epidural steroid injections on bone mineral density and bone turnover markers in patients taking anti-osteoporotic medications. *Pain Physician*. 2018;21:E435-E447.
49. Al-Shoha A, Rao DS, Schilling J, Peterson E, Mandel S. Effect of epidural steroid injection on bone mineral density and markers of bone turnover in postmenopausal women. *Spine*. 2012;37:E1567-E1571.
50. Kim S, Hwang B. Relationship between bone mineral density and the frequent administration of epidural steroid injections in postmenopausal women with low back pain. *Pain Res Manag*. 2014;19:30-34.
51. Kang SS, Hwang BM, Son H, Cheong IY, Lee SJ, Chung TY. Changes in bone mineral density in postmenopausal women treated with epidural steroid injections for lower back pain. *Pain Physician*. 2012;15:229-236.
52. Kim YU, Karm MH, Cheong Y, et al. Effect of epidural steroid injection on bone mineral density in postmenopausal women according to antiosteoporotic medication use. *Pain Physician*. 2016;19:389-396.
53. Mandel S, Schilling J, Peterson E, Rao DS, Sanders W. A retrospective analysis of vertebral body fractures following epidural steroid injections. *J Bone Joint Surg Am*. 2013;95:961-964.
54. Yi Y, Hwang B, Son H, Cheong I. Low bone mineral density, but not epidural steroid injection, is associated with fracture in postmenopausal women with low back pain. *Pain Physician*. 2012;15:441-449.
55. Shin CS, Kim MJ, Shim SM, et al. The prevalence and risk factors of vertebral fractures in Korea. *J Bone Miner Metab*. 2012;30:183-192.
56. Manchikanti L, Pampati V, Beyer C, Damron K, Cash K, Moss T. The effect of neuraxial steroids on weight and bone mass density: a prospective evaluation. *Pain Physician*. 2000;3:357-366.
57. Liu Y, Carrino JA, Dash AS, et al. Lower spine volumetric bone density in patients with a history of epidural steroid injections. *J Clin Endocrinol Metab*. 2018;103:3405-3410.
58. Szokol JW, Gilbert HC. A herpes zoster outbreak temporarily associated with an epidural steroid injection. *Reg Anesth Pain Med*. 1998;23:328.
59. Parsons SJ, Hawboldt GS. Herpes zoster: a previously unrecognized complication of epidural steroids in the treatment of complex regional pain syndrome. *J Pain Symptom Manage*. 2003;25:198-199.
60. Browning DJ. Acute retinal necrosis following epidural steroid injections. *Am J Ophthalmol*. 2003;136:192-194.
61. Berbari EF, Hanssen AD, Duffy MC, et al. Risk factors for prosthetic joint infection: case-control study. *Clin Infect Dis*. 1998;27:1247-1254.
62. Kaspar S, de V de Beer J. Infection in hip arthroplasty after previous injection of steroid. *J Bone Joint Surg Br*. 2005;87:454-457.
63. Papavasiliou AV, Isaac DL, Marimuthu R, Skyrme A, Armitage A. Infection in knee replacements after previous injection of intra-articular steroid. *J Bone Joint Surg Br*. 2006;88:321-323.
64. Schairer WW, Nwachukwu BU, Mayman DJ, Lyman S, Jerabek SA. Preoperative hip injections increase the rate of periprosthetic infection after total hip arthroplasty. *J Arthroplasty*. 2016;31:166-169. e1.
65. Chambers AW, Lacy KW, Liow MHL, Manalo JPM, Freiberg AA, Kwon YM. Multiple hip intra-articular steroid injections increase risk of periprosthetic joint infection compared with single injections. *J Arthroplasty*. 2017;32:1980-1983.
66. Yang S, Werner BC, Cancienne JM, et al. Preoperative epidural injections are associated with increased risk of infection after single-level lumbar decompression. *Spine J*. 2016;16:191-196.
67. Seavey JG, Balazs GC, Steelman T, Helgeson M, Gwinn DE, Wagner SC. The effect of preoperative lumbar epidural corticosteroid injection on postoperative infection rate in patients undergoing single-level lumbar decompression. *Spine J*. 2017;17:1209-1214.
68. Asomugha EU, Miller JA, McLain RF. Surgical site infections in posterior lumbar surgery: a controlled-cohort study of epidural steroid paste. *Spine*. 2017;42:63-69.
69. Singla A, Yang S, Werner BC, et al. The impact of preoperative epidural injections on postoperative infection in lumbar fusion surgery. *J Neurosurg Spine*. 2017;26:645-649.
70. Baloch N. 'Steroid psychosis': a case report. *Br J Psychiatry*. 1974;124:545-546.
71. Benyamin RM, Vallejo R, Kramer J, Rafeyan R. Corticosteroid induced psychosis in the pain management setting. *Pain Physician*. 2008;11:917-920.
72. Robinson DE, Harrison-Hansley E, Spencer RF. Steroid psychosis after an intra-articular injection. *Ann Rheum Dis*. 2000;59:927.
73. Sinha ADM, Kothari G. Manic episode following epidural steroid injection: a case report. *PM R*. 2013;9:s310-s311.
74. Maes M, Meltzer HY, Stevens W, Cosyns P, Blockx P. Multiple reciprocal relationships between in vivo cellular immunity and hypothalamic-pituitary-adrenal axis in depression. *Psychol Med*. 1994;24:167-177.
75. Karp JF, Yu L, Friedly J, Amtmann D, Pilkonis PA. Negative affect and sleep disturbance may be associated with response to epidural steroid injections for spine-related pain. *Arch Phys Med Rehabil*. 2014;95:309-315.
76. Laroche M, Arlet J, Mazieres B. Osteonecrosis of the femoral and humeral heads after intraarticular corticosteroid injections. *J Rheumatol*. 1990;17:549-551.
77. Weitoft T, Larsson A, Ronnblom L. Serum levels of sex steroid hormones and matrix metalloproteinases after intra-articular glucocorticoid treatment in female patients with rheumatoid arthritis. *Ann Rheum Dis*. 2008;67:422-424.
78. Gitkind AI, Shah B, Thomas M. Epidural corticosteroid injections as a possible cause of menorrhagia: a case report. *Pain Med*. 2010;11:713-715.
79. Danielson KD, Harrast MA. Focal spinal epidural lipomatosis after a single epidural steroid injection. *PM R*. 2011;3:590-593.
80. Tok CH, Kaur S, Gangi A. Symptomatic spinal epidural lipomatosis after a single local epidural steroid injection. *Cardiovasc Intervent Radiol*. 2011;34(suppl 2):S250-S255.
81. McCullen GM, Spurling GR, Webster JS. Epidural lipomatosis complicating lumbar steroid injections. *J Spinal Disord*. 1999;12:526-529.

82. Boonen S, Van Distel G, Westhovens R, Dequeker J. Steroid myopathy induced by epidural triamcinolone injection. *Br J Rheumatol*. 1995;34:385-386.

83. Chen YC, Gajraj NM, Clavo A, Joshi GP. Posterior subcapsular cataract formation associated with multiple lumbar epidural corticosteroid injections. *Anesth Analg*. 1998;86:1054-1055.

Disclosure

A.S. Evergreen Healthcare, 12039 NE 128th St Suite 500, Kirkland, WA 98034. Address correspondence to: A. S.; e-mail: sportsandspinedoc@yahoo.com
Disclosure: nothing to disclose

J.F. Department of Rehabilitation Medicine, University of Washington, Seattle, WA
Disclosure: nothing to disclose

C.J.S. Department of Physical Medicine and Rehabilitation, University of Pittsburgh Medical Center, Pittsburgh, PA
Disclosure: nothing to disclose

Submitted for publication August 16, 2018; accepted October 18, 2018