Corticosteroid Injections for Non-spinal Musculoskeletal Conditions: Consideration of Local and Systemic Adverse Drug Reactions and Side Effects

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ABSTRACT

Following specialist training, physiotherapists in some countries, such as the United Kingdom and Norway perform landmark, and ultrasound guided, soft tissue and joint injections for a wide range of musculoskeletal conditions. Whether they inject or not, physiotherapists may wish to recommend injections, and people requiring care commonly seek physiotherapists' opinions on injection therapy. Globally, there has been a substantial increase in the use of corticosteroid injections to treat musculoskeletal conditions. Those performing injections or providing advice need be cognisant of the possible harms of the procedures and communicate this information sensitively to those considering the procedures. This review synthesises evidence for local and systemic adverse reactions and side effects related to corticosteroid injections in the treatment of non-spinal musculoskeletal conditions. Multiple databases including PubMed, Medline, PEDro, and Cinahl were searched, and all levels of evidence were included if they added to the review. Serious adverse events appear to be rare, possibly in part due to under-reporting of side effects. Where available, suggestions for minimising risk and aftercare have been made. As substantial gaps in the evidence were found, areas for further research are suggested and a decision-making tool is included to facilitate whether to proceed to injection, proceed with precaution, or no injection.

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INTRODUCTION

Corticosteroid injections (CSI) are commonly used in the management of musculoskeletal conditions involving symptoms related to joints and soft tissues in both athletic and non-athletic populations. In the United Kingdom (UK) physiotherapists, rheumatologists, radiologists, pain specialists, nurses, sports and exercise doctors, and orthopaedic surgeons perform injections as either image or landmark guided interventions. Although the use of CSIs is increasing, knowledge of their effectiveness in musculoskeletal pain conditions, together with associated adverse events and side effects, remains equivocal (Stout et al., 2019). Adverse drug reactions cost the UK National Health Service (NHS) £446 million a year (Patton & Borshoff, 2018) and in the United States of America (USA) approximately USD $30.1 billion dollars (Sultana et al., 2013).

The aim of this paper was to support shared decision making by clinicians and patients by synthesising evidence for local and systemic adverse reactions and side effects related to CSIs in the management of upper and lower limb musculoskeletal conditions.

METHODS

A formal search strategy was not used and is acknowledged as a possible limitation of the study. Eight co-authors contributed and performed a search that was designed to cover their area of expertise. Systematic reviews with and without meta-analysis, randomised and pseudo-randomised trials, cohort studies, case control, cases series, and case studies published in the English language were considered. Both retrospective and prospective evidence were included. Search terms included "corticosteroid injection", "adverse reaction/event", "side effect", and "musculoskeletal condition(s)". Databases searched were Scopus, Web of Science, PubMed, Medline, DOAJ, PEDro, and Cinahl. Eligibility for inclusion was the administration of a CSI used to treat non-spinal musculoskeletal conditions, either as a stand-alone treatment, or compared to another intervention, where adverse events and/or side effects were reported. Exclusion included CSIs for spinal and non-musculoskeletal conditions.

FINDINGS

The information extracted from the papers included in this manuscript is presented in the following sections, and includes *the pharmacology of corticosteroids*, *history of injections*, *definitions of side and adverse effects*, and *descriptions of local and systemic adverse drug reactions and side effects*.

The pharmacology of corticosteroids

The adrenal glands are endocrine glands, located above the kidneys and are involved in the production of hormones. The outer adrenal cortex produces three corticosteroid hormones (steroidogenesis): (i) mineralocorticoids that regulate blood pressure and electrolyte balance, (ii) androgens that are involved in reproduction, and (iii) glucocorticoids that regulate functions including glucose metabolism, cognition, skeletal growth, and inflammation (Ramamoorthy & Cidlowski, 2016). The term glucocorticoid is a synthesised word: **glu**cose + **cor**tex + ster**oid**. The circadian release of glucocorticoids is regulated by the hypothalamic–pituitary–adrenal axis. Cortisol is a human glucocorticoid and functions to increase blood sugar and suppress the immune system. Its release is increased in response to stress and low blood-glucose. Sustained high levels of cortisol may lead to an allostatic load (McEwen & Stellar, 1993) and is associated with multiple health concerns. Synthetic cortisol is known as hydrocortisone and a range of synthetic glucocorticoids are among the most widely prescribed drugs worldwide (Ramamoorthy & Cidlowski, 2016). The action of glucocorticoids is mediated by the intracellular glucocorticoid receptor (IGR) and once bound to this receptor mediates myriad effects (Ramamoorthy & Cidlowski, 2016). Several mechanisms have been proposed that lead to a reduction in inflammation including inhibition of pro-inflammatory genes that encode cytokines and cell adhesion (Cruz-Topete & Cidlowski, 2015). However, glucocorticoids can also induce a pro-inflammatory response, suggesting their action is very complex and not yet fully understood (Cruz-Topete & Cidlowski, 2015).

History of injections

From the 1600s the term injection was used to describe the process of driving a fluid into a body using a purpose-built tool. As such, the first to perform injections were Indigenous or First Nation populations who used blowpipes to *inject* poisons. Christopher Wren is credited with fashioning a "syringe" from a quill and bladder to inject dogs with alcohol and opium in the 17th century. In 1807 the Edinburgh Medical and Surgical dictionary defined a syringe as "A well-known instrument, serving to imbibe or suck in a quantity of fluid and afterwards expel the same with violence. A syringe is used for transmitting injections into cavities or canals." In the 20th century references relating to injections of salvarsan (arsphenamine) for syphilis (1911), heroin for non-medical use (1925), and analgesics for musculoskeletal pain conditions (1944) were published.

Steinbrocker (1944) reported:

> Analgesic therapy with procaine hydrochloride … is being widely employed in a variety of painful disorders and has established its effectiveness in many of them. Its field of usefulness has been steadily extended recently, particularly in acute and chronic musculoskeletal conditions—fibrositis (myositis), bursitis, neuritis and some arthritides. Although every practitioner or student of these diseases must encounter some apparently suitable patients whose stubborn symptoms fail to respond to procaine or alcohol block, confusing differences in therapeutic results have been recorded by various investigators. The mere insertion of a needle somewhere in the region of pain, without introducing analgesic solutions, also has been reported to give frequent lasting relief (p. 397).

Murnaghan and McIntosh (1955) described further uncertainty regarding CSI, as no differences in outcome for people diagnosed with painful shoulders injected with hydrocortisone (n = 24) or lignocaine (n = 27) were reported. They concluded it was doubtful whether hydrocortisone has any special effect. Despite this uncertainty, corticosteroid injections became widely used to treat athletes in the 1960s (Nicols, 2005).

Injection therapy principally involves corticosteroid in isolation or in combination with anaesthetic. Naturally occurring cortisone and manufactured corticosteroids have a pharmacological effect by inhibiting granular tissue formation, ground substance

sulfation, fibroblast and blood vessel formation, and collagen tissue repair (Nicols, 2005).

Data from the National Health Service (NHS, UK) suggest that approximately 800,000 prescriptions for injectable corticosteroids are dispensed annually. The shoulder, accounting for over one-third of injections, is the most common region injected and the most common shoulder injection (72% of all shoulder injections) is for rotator cuff-related shoulder pain (Cook et al., 2018).

Due to the cost, uncertainty, short-lived clinical benefit, and potential harms, high numbers of injections are of concern (Cook et al., 2018; Hoffmann et al., 2020; Mohamadi et al., 2017). For example, randomised clinical trial results suggest worse outcomes at one year for CSI in the treatment of tennis elbow when compared to placebo (Coombes et al., 2013). Intra-articular CSI at the time of knee arthroscopy increases the risk of post-operative infection (Kohls et al., 2022), and early findings suggest that CSI for knee osteoarthritis may contribute to worsening of the condition as reported in MRI scans (Bharadwaj, 2022) and radiography (Darbandi, 2022).

Definitions of adverse events, adverse reactions, and side effects

Following the review of the included literature, adverse events, adverse reactions, and side effects were defined and are presented in Table 1.

Adverse drug reactions and side effects

Following the review of the included literature, adverse drug reactions and side effects were extracted and formatted into two tables. Table 2 details *local* adverse drug reactions and side effects, and Table 3 details *systemic* adverse drug reactions and side effects.

Other systemic effects

Myopathy

Myopathy refers to a clinical disorder of skeletal muscle. Two forms, acute and chronic, were discussed in the literature. *Chronic steroid myopathy* typically affects the proximal lower limbs (Minetto et al., 2011) and to a lesser extent the bulbar and respiratory muscles (Haran et al., 2018). Glucocorticoid-induced myopathy was first described in 1932 in people diagnosed with Cushing's syndrome (Pereira & Freire de Carvalho, 2011). The pathogenesis is complex as glucocorticoids have a catabolic effect on muscle, negatively impacting on protein synthesis and increasing protein catabolism resulting in muscle atrophy (Pereira & Freire de Carvalho, 2011). Daily doses more of than 40 to 60 mg/day of prednisone or its equivalent can induce clinically important weakness within two weeks (Paik, 2022). Muscle weakness is also a sign of adrenal insufficiency and overall steroid dosage should be accounted for.

Acute steroid myopathy (ASM) is very rare (fewer than 20 cases have been reported in literature), but needs to be considered as a plausible adverse effect of steroid injection therapy as it could occur with dosages normally used to treat musculoskeletal conditions (Haran et al., 2018). ASM is unpredictable, heterogeneous and can develop 1–3 days after a single 1mg Betamethasone intramuscular injection (Sun & Chu, 2017). The withdrawal of corticosteroids leads to gradual full recovery over several weeks in most patients (Haran et al., 2018). Before

Table 1

Definitions of Adverse Events, Adverse Reactions, and Side Effects

Term	Definition
Adverse event	An *adverse event* is an iatrogenic incident that results in harm (mild, moderate) to an individual because of a medical procedure (assessment or intervention).
Serious adverse event	A *serious adverse event* occurs when the iatrogenic incident results in severe and life-threatening harm, hospitalisation, prolongation of existing hospitalisation, significant disability or incapacity, or death.
Adverse drug reaction	An *adverse drug reaction* (ADR) has been defined as "A response to a drug that is noxious and unintended and that occurs at doses normally used for prophylaxis, diagnosis, or treatment of disease, or for modification of physiological function" (Tan et al., 2014, p. 2). An ADR may be a known effect, or a new and previously unrecognised effect of a drug (Medicines and Healthcare Products Regulatory Agency, 2006). An ADR may occur *locally* at the site of the injection, (e.g., hypopigmentation and subcutaneous fat, muscle atrophy following a wrist injection), distally, away from the site of the injection (e.g., increased intraocular pressure following intra-articular knee injection), or *systemically* (e.g., hyperglycaemia in people with diabetes mellitus following intra-articular steroid injections) (Taliaferro et al., 2018).
Side effect	The term *adverse reaction*, also known as *toxic effect* or *side effect*, refers to an unwanted effect experienced by an individual, caused by the drug (Aronson & Ferner, 2005). A *side effect* is defined as: Any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the medicine. Such effects may be either positive or negative. Such effects may be well-known and even expected and may require little or no change in patient management.

Table 2

Local Adverse Drug Reactions and Side Effects

Local adverse drug reaction/side effect	Drug/dose	Region of injection/ condition	Incidence	Study type (reference)	Summary of findings
Tendon rupture (rotator cuff full thickness tear)	Triamcinolone acetate 40mg	Shoulder	17% (66% with a pre-existing partial thickness tear)	Prospective, open label clinical trial (Ramírez et al., 2014)	CS-induced tendon rupture may be associated with suppression of tenocyte activity and collagen synthesis (Wong et al., 2004). Tendon rupture associated with local and systemic CS (Kotnis et al., 1999). Ruptures reported in the Achilles, long head of biceps, extensor digitorum, and patellar tendons (Halpern et al., 1977). 17% of 53 participants without evidence of FTRCTs who received 40 mg triamcinolone acetate for subacromial pain developed FTRCTs in one week; the majority (66%) occurred in the presence of a PTT pre-injection (Ramírez et al., 2014). Lack of blinding between the ultrasonographer and the participants may have confounded the findings. Triamcinolone acetonide may be related to more structural defects and ruptures than methylprednisolone. In addition, ruptures may be related to multiple injections at a site (Nicols, 2005). Definitive causation has not been demonstrated.
Cartilage thinning	Triamcinolone acetate 40mg (every 3 months over 2 years)	Knee joint	Not stated	Randomised, placebo, double blind clinical trial (McAlindon et al., 2017)	Urinary crosslinked C-telopeptide of type II collagen (uCTX-II), associated with degenerative cartilage breakdown, is a biomarker found in urine and provides valuable information of the effects of corticosteroids on cartilage (Klocke et al., 2018). The certainty by which CSI are associated with cartilage damage is equivocal and opposing findings have been published. Following a single dose of 40 mg triamcinolone acetonide, uCTX-II levels were reduced at three weeks when compared to a saline group, suggesting a protective effect of corticosteroid on cartilage (Klocke et al., 2018). This is supported by a systematic review of human and animal in-vitro studies, reporting that after low doses of CSI (2–3 mg to 8–12 mg), cartilage cells were synthesised and degenerative enzymes inhibited (Wernecke et al., 2015). CS may reduce the rate of degenerative changes in osteoarthritic joints where inflammation is part of the degenerative process (Ayral et al., 2005). In higher doses corticosteroids may induce chondrocyte apoptosis, decrease cell viability, suppress the expression of matrix proteins, or promote calcium pyrophosphate dihydrate crystals formation that may accelerate cartilage degeneration (Zeng et al., 2019). A systematic review concluded that higher and more sustained exposure (> 3mg/dose or 18–24 mg/cumulative dose) was associated with gross cartilage damage and chondrotoxicity in human and animal in-vitro studies (Wernecke et al., 2015). Following sustained and repeated CSI, a reduction in joint space on MRI scan was found in the CS group compared to patients injected with saline (McAlindon et al., 2017). It is important to note that following the injection, the decrease in knee pain across the treatment groups did not significantly differ.

Local adverse drug reaction/side effect	Drug/dose	Region of injection/ condition	Incidence	Study type (reference)	Summary of findings
					Higher dose, more frequently administered injections may lead to progression of osteoarthritis as radiographic changes correlate with increased pain and loss of function (Hill et al., 2007; Shah et al., 2019; Van Spil et al., 2015) and may increase the risk of progression to total knee replacement (Liu et al., 2018; Zeng et al., 2019). Confounding variables are likely to exist in such studies and it is worth considering the contribution of phenotype in relation to osteoarthritis disease progression. For example, as body mass index, sedentary lifestyle, sex, ethnicity, age, pain, and diet are risk factors associated with arthritis (Karsdal et al., 2015; Musumeci et al., 2015). Limiting the frequency of injections has been advocated (Walker-Bone et al., 2004), but this appears to be based on professional opinion as opposed to definitive research evidence (Douglas, 2012). Current recommendations are that injections should be limited to once every 3–4 months and not exceed 3–4 injections per year (National Institute for Health and Care Excellence, 2017) (Lane & Thompson, 1997; Neustadt, 2006).
Infection/septic arthritis	Not stated	Not stated	1:3,000–1:100,000	Survey (Baima & Isaac, 2008 Narrative review (Peterson & Hodler, 2011; Shah et al., 2019 Retrospective cohort (Charalambous et al., 2003; Holland et al., 2012)	Bacterial or septic arthritis is a rare but potentially catastrophic complication following CSI (Shah et al., 2019), with a 15% mortality rate. In survivors, impairment of joint function occurs in up to 50% of cases (Charalambous et al., 2003). Early symptoms may include severe local pain, heat, swelling, feeling systemically unwell, temperature, nausea, dizziness, and fatigue. Faulty aseptic technique is probably the main cause (Holland et al., 2012; von Essen & Savolainen, 1989), but may occur due to hormonal activation of a previously quiescent infection (von Essen & Savolainen, 1989). Staphylococcus aureus is most implicated (Charalambous et al., 2003; Provenzano et al., 2018). Pre-injection blood screening may be relevant for some patients. Pre-injection screening for previous joint surgery, pre-existing joint disease, particularly rheumatoid arthritis as the immune system is already compromised, diabetes mellitus, the presence of prosthetic or osteosynthetic material, skin defect or infection, advanced age, and immunosuppressive medication (Kaandorp et al., 1995) is essential.
Post-injection pain (PIP)	Depomedrone 40 or 80 mg	Shoulder Trigger finger DeQuervain's tenosynovitis	1–81%	Systematic review (Brinks et al., 2010). Prospective cohort (Fawi et al., 2017) Randomised controlled clinical trial (Goldfarb et al., 2007)	PIP is a self-limiting increase in pain (+/- swelling) by 2 or more points on a 10-point VAS (Goldfarb et al., 2007; Peterson & Hodler, 2011; Shah et al., 2019). Proposed mechanisms may include steroid microcrystals (Shah et al., 2019) and a reaction caused by the "rapid intracellular ingestion of the microcrystalline steroid ester" (Berger & Yount, 1990, p. 1286). Acidity of the injection may result in short-term inflammation, pain, and crystal induced synovitis (Goldfarb et al., 2007). PIP may also be due to physical trauma to tissues during the procedure, nocebo, insufficient post procedure relative rest, and natural history. To minimise PIP, analgesics, non-pharmacological pain relief methods, and avoidance of strenuous activities should be considered for at least 48 hr after an injection.

Local adverse drug reaction/side effect	Drug/dose	Region of injection/ condition	Incidence	Study type (reference)	Summary of findings
Subcutaneous fat atrophy	Triamcinolone acetate 10–40 mg	De Quervain's tenosynovitis Tennis elbow	1.5–40%	Systematic review (Brinks et al., 2010)	Subcutaneous fat and skin atrophy (lipoatrophy) and hypopigmentation are considered serious adverse reactions following a corticosteroid injection into soft tissue. Lymphatic spread of corticosteroid into the dermal and epidermal tissues has been hypothesised as the mechanism (Evans & McGibbon, 2002; Nanda et al., 2006), but the definitive cause remains unknown. Lipoatrophy has been reported with methylprednisolone acetate injections (Beyzadeoglu et al., 2011), but may be more common in high doses of corticosteroids and with triamcinolone acetonide due to its larger molecular size and longer half-life (Kim, Lee et al., 2015). Fat atrophy usually affects more superficial regions such as the wrist, hand, elbow, ankle, and foot. The incidence of post-injection fat atrophy has been reported between 0.6%–40% (Brinks et al., 2010; Kim, Lee et al., 2015). It usually appears within two weeks to 4 months (Ghunawat & Sarkar, 2018; Green et al., 2019; Liang & McElroy, 2013; Park et al., 2013; Wang, 2017), and typically (but not always) resolves within 6–30 months (Ghunawat & Sarkar, 2018; Green et al., 2019; Kim, Lee et al., 2015; Martins et al., 2019; Park et al., 2013).
Hypopigmentation	Triamcinolone acetate 10 mg	De Quervain's tenosynovitis Tennis elbow	1.3–4%	Systematic review (Brinks et al., 2010)	Hypopigmentation is characterised by a lightening in skin colour, mostly affecting the peripheral cutaneous regions possibly due to thinner dermal layers. It affects 1–4% of adults (Papadopoulos & Edison, 2009; Park et al., 2013), and is more noticable in people with darker skin colour (Ghunawat & Sarkar, 2018). It is proposed that steroids inhibit prostaglandins or cytokines involved in melanin production (Gupta et al., 2006). Re-pigmentation occurs as melanocytes are downregulated (Green et al., 2019). Strategies to reduce fat atrophy and hypopigmentation include: The use of CS with smaller molecular size and shorter half-life such as methylprednisolone. Using triamcinolone acetate for deep structures such as the knee and shoulder joints (Kim, Lee et al., 2015; Liang & McElroy, 2013; Park et al., 2013). A RCT comparing USGI to a landmark guided injection for DeQuervain's tenosynovitis found fewer cases of hypopigmentation in the USGI group (Roh et al., 2018). Compression over the injection site to reduce the chances of steroid "leaking" along the needle track may also reduce the risk (Papadopoulos & Edison, 2009; Park et al., 2013).

Note. CS = corticosteroid; CSI = corticosteroid injections; FTRCT = full thickness rotator cuff tear; MRI = magnetic resonance imaging; PTT = partial thickness tears; RCT = randomised controlled trial; USGI = ultrasound guided injection; VAS = visual analogue scale.

considering a corticosteroid injection, clinicians are advised to consider no injection where there is a history of long-term steroid use.

Glaucoma

Glaucoma is associated with loss of vision due to raised pressure on the optic nerve. The condition is a leading cause of blindness globally, and in the UK approximately 2% of the population over 40 years of age have glaucoma. Corticosteroids increase intraocular pressure (IOP), cause optic disc cupping, optic nerve atrophy, and glaucomatous visual field loss (Tripathi et al., 1999) and corticosteroid-induced glaucoma following corticosteroid injection (Schäcke et al., 2002). In patients with established glaucoma, a further dangerous increase of the intraocular pressure due to corticosteroid therapy may often be problematic (Schäcke et al., 2002). Symptoms include sudden onset of blurred vision leading to unexpected short-term blurred vision or vision loss, with potential irreversible loss of vision.

Increased IOP typically returns to normal after 2–4 weeks but can persist for over 12 months (Spaeth et al., 1977). Approximately 18–36% of the general population show a moderate increase of 5mm Hg or more IOP after topical administration of corticosteroids with 5–6% of the general population, and 46–92% of patients with primary open-angle glaucoma (POAG), experiencing a significant and potentially damaging rise in IOP after topical glucocorticoid administration (Tripathi et al., 1999).

One suggestion to explain the mechanism by which corticosteroids may lead to worsening signs of glaucoma is exposure to corticosteroids in vitro show increases in ocular cell size and production of a glycoprotein myocilin that may lead to primary open angle glaucoma (POAG) (Tamm, 2002). The heterogeneous nature of the response of corticosteroid-induced ocular hypertension indicates that other factors could have a possible role. Elevated IOP has been noted in patients with Cushing's syndrome secondary to adrenal adenoma, carcinoma, or adrenal hyperplasia (Huschle et al., 1990). First-degree relatives of patients with POAG, diabetes, high myopia, and with connective tissue diseases (especially rheumatoid arthritis) are more likely to develop increased IOP after corticosteroid treatment than the normal population (Manjiani et al., 2015). If symptoms of visual disturbances, especially bilateral blurred vision, are experienced, an urgent medical or ophthalmologist referral is mandatory (Manjiani et al., 2015).

Glaucoma may affect people of all ages, but is more common in older people, and is more common in people of Afro-Caribbean, Afro-American, Hispanic, and African descent. It is more common in near-sighted people and people with high blood pressure, thin corneas, and diabetes. For people at higher risk, or for people over the age of 50 years, an eye examination (if not conducted recently) to exclude glaucoma should be considered prior to a CSI.

DISCUSSION

This review has highlighted a series of diverse side effects and adverse events that are associated with corticosteroid injections for musculoskeletal joint and soft tissue injections. These are presented in Tables 2 and 3. The review has also highlighted the paucity and incomplete nature of knowledge surrounding this practice. The global healthcare community needs to address this, and Table 3 offers non-exhaustive suggestions for research to address these deficits.

The review revealed shortcomings in our knowledge with respect to short-, medium-, and long-term consequences of CSI injection therapy. This should be presented to patients considering injection therapy as part of the shared decision-making process. Table 4 details information that should be discussed with patients considering an injection for rotator cuff-related shoulder pain as part of this process.

Based on the information generated in this review, a clinical decision-making tool was developed to support clinicians in their decision to proceed to injection, proceed with caution (and possibly consider other interventions first), or not to inject. This is presented as an algorithm in Figure 1.

CONCLUSION

There has been an exponential increase in the use of corticosteroid injections to treat musculoskeletal conditions. This has not kept pace with knowledge necessary to inform clinicians and those considering injections on the potential benefits and possible harms, which include local and systemic adverse drug reactions and side effects. Our cumulative knowledge is predominantly based upon studies considered to be of high risk of bias, retrospective analyses, case studies, and systematic reviews synthesising inadequate primary data. Serious adverse events appear to be rare, but this may be due to under-reporting of side effects. There is unquestionably a definitive lack of understanding of the depth and breadth of local adverse drug reactions. This poses a dilemma for clinicians wanting to reach a balanced clinical decision as to whether the benefits of an injection outweigh harm. This needs to be addressed and clinicians recommending and providing injection therapy have a duty of care to fill the large voids in our knowledge.

We advocate that prior to a CSI an in-depth health history should be undertaken with a focus on existing comorbidities such as diabetes and previous or concurrent steroid use. Screening for systemic infection, glaucoma, a history of mental illness, and diabetes, must be included. We recommend providing the Steroid Emergency Card following a third injection within a 12-month period (NHS, 2020).

KEY POINTS

1. Local and systemic adverse drug reactions and side effects are associated with corticosteroid injections for musculoskeletal conditions involving the upper and lower limbs.
2. Intended benefits and potential harms need to be communicated with people considering these procedures.
3. Shared decision-making supports people considering corticosteroid injections to understand the intended benefits and potential harms associated with the procedures.
4. This review has clearly illustrated substantial deficits in knowledge relating to most aspects of injection therapy for non-rheumatological musculoskeletal conditions. These should be addressed in RCTs and large cohort studies and require international collaboration.

Table 3

Systemic Adverse Drug Reactions and Side Effects

Systemic adverse drug reaction/side effect	Drug/dose	Region of injection/ condition	Incidence	Study type (reference)	Summary of findings
Elevated blood glucose	Methylprednisolone/80 mg Triamcinolone hexacetonide/ 20 mg or Triamcinolone acetate/40 mg	Subacromial region in people with diabetes Knee osteoarthritis in people with diabetes	100%	Prospective case study (Aleem, 017) Prospective controlled study (Habib & Miari, 2011)	CS reduce cell wall sensitivity to insulin by blocking insulin receptor sites, resulting in the cell wall becoming temporarily insulin resistant causing a rise in blood glucose levels (BGL) (Hwang & Weiss, 2014). HbA1c is a measure of BGL over a 3-month period (Kim, Schroeder et al., 2015) and a HbA1c < 7 mg/dL is indicative of well controlled diabetes (Hwang & Weiss, 2014). One study compared HbA1c in different diabetic groups and found that following an injection of 2 ml of 40 mg (80 mg) methylprednisolone acetate to the subacromial space, there was a mean rise in BGL of 38 mg/dL in the well-controlled diabetic group compared to 98 mg/dL in the poorly controlled group (Aleem, 2017). BGL were reported to increase (range 125 mg/dL to 320 mg/dL and in one instance increased to 518 mg/dL) in people with diabetes following CSI (Waterbrook et al., 2017). Elevated BGL may occur 2 hr post injection (Uboldi et al., 2009), but usually between 1 and 2 days post CSI (Moon et al., 2014; Twu et al., 2018), and return to baseline BGL after several days especially in those with poorly controlled diabetes (Aleem, 2017). Lower dose steroids were generally associated with a quicker return to baseline BGL (Patel et al., 2015; Twu et al., 2018). Patients with HbA1c > 7 mg/dL are at greater risk of hyperglycaemia and close monitoring is essential to reduce the chances of further diabetic impairment.
Adrenal suppression	Methylprednisolone/80 mg	Knee osteoarthritis	25%	Randomised controlled study (Habib et al., 2014)	Adrenal insufficiency (AI) occurs when the adrenal glands do not produce enough cortisol, which may be a consequence of oral, inhaled, or injected CS. Cortisol is a steroid hormone that helps the body respond to stress, control blood sugar levels and blood pressure, regulates metabolism, reduces inflammation, and aids with memory formulation. CS suppress the hypothalamic pituitary adrenal axis suppressing the adrenal glands to reduce production of adrenocorticotropic hormone leading to low levels of cortisol production (Stout et al., 2019). Characteristic clinical features of AI are unintentional weight loss, anorexia, postural hypotension, fatigue, muscle, and abdominal pain (Husebye et al., 2021). In the management of rheumatoid arthritis, 52.2% of patients had reduced adrenocorticotropic hormone levels when CS was administered by intra-articular injections and steroids administered via the nasal route for rheumatic disorders compared to 4.2% when administered nasally (Broersen et al., 2015). Nine out of 10 athletes had reduced cortisol levels 14 days after cortivazol/betamethasone injection (Duclos et al., 2007). Raised biomarkers relating to adrenal suppression were found in 25% of people 4 weeks after an injection of 80 mg methylprednisolone for knee osteoarthritis (Habib et al., 2014). A single knee injection of 40 mg methylprednisolone resulted in significantly reduced cortisol levels 24 hr post-injection and below normal levels at 72 hr (Lazarevic et al., 1995). The clinical significance of this remains unclear (Paragliola et al., 2017). Higher doses of depomedrone are associated with lower cortisol levels (Mader et al., 2005) and repeated intra-articular injections may lead to adrenal suppression particularly when the course of steroids ceases (Paragliola et al., 2017). Risk reduction includes a 30-day interval between injections (Johnston et al., 2015) and refraining from excessive heat, altitude, dehydration, over-exertion, trauma, or surgery post injection (Freire & Bureau, 2016).

Systemic adverse drug reaction/side effect	Drug/dose	Region of injection/ condition	Incidence	Study type (reference)	Summary of findings
					Concomitant use of corticosteroids with anti-retroviral drugs such as ritonavir have resulted in cases of significant adrenal insufficiency (Husebye et al., 2021). Ritonavir blocks the enzyme pathway CYP3A4, which raises concentrations of medications that are metabolised using the same pathway, including corticosteroids (Wood et al., 2015). In some cases, injections were preceded by a course of inhaled steroids for chronic obstructive airways disease and the addition of the injected steroid caused the accumulation of steroid systemically (Alidoost et al., 2020). Clinicians are recommended to use a drug interaction checker such as that from the University of Liverpool (2023). Gradual steroid withdrawal is often the best management option (Husebye et al., 2021; Wood et al., 2015). The use of the "steroid emergency card" is advocated for those on long-term steroids receiving exogenous steroid injections (NHS, 2020).
Menstrual alterations	Triamcinolone acetate/40 mg	Frozen shoulder	24%	Randomised trial (Van der Windt et al., 1998)	Corticosteriods may initiate a negative feedback loop involving the hypothalamic–ovarian axis leading to a suppression of hormones (Gitkind et al., 2010). Triamcinolone acetonide appears to have a high affinity to progesterone receptors (Yoon & Lee, 2009) as depleted levels of dehydroepiandrosterone, testosterone, and oestradiol were found in blood serum analysis following an intra-articular injection of 20 mg triamcinolone hexacetonide for knee rheumatoid arthritis (Weitoft et al., 2008). Over 50% of premenopausal women reported a menstrual disturbance including longer duration of menses and increased blood flow after an injection for peripheral joint or soft tissue pain (Mens et al., 1998). Although there is a paucity of definitive data, one study reported that 16% of women reported changes in menses following an intra-articular shoulder injection of 40 mg triamcinolone (Van der Windt et al., 1998). A case series reported that post-menopausal women experienced bleeding between 9 and 19 days after shoulder, knee, or bursal injections with doses ranging from 10–40 mg triamcinolone acetate. Those between the ages of 45 to 64 years were more likely to report bleeding compared to the over 65-year age group (4.5/1000 ~ 3.3/1,000), which may be due to greater degree of atrophic endometrium in the older age group (Gowri, 2013). Information should be provided as those who experience menstrual alterations may not relate it to the CS injection and may seek specialist advice (Suh-Burgmann et al., 2013).
Facial flushing	Triamcinolone acetate/40 mg Triamcinolone acetate/40 mg or Triamcinolone hexacetonide/ 20 mg	Knee	12.5–40%	Prospective randomised trial Jacobs et al., 1991) Comment (Pattrick & Doherty, 1987)	Facial flushing is associated with erythema (and warmth) that affects the face and upper trunk (Pattrick & Doherty, 1987) and is a relatively minor complication of corticosteroid injections. It is thought to be histamine-mediated, or an immunoglobulin mediated mechanism (Everett et al., 2004) lasting last less than 24 hr post injection (Jacobs et al., 1991). Facial flushing may be more common following epidural injections but has been reported following intra-articular knee injections (Pattrick & Doherty, 1987) and after injections for frozen shoulder (Jacobs et al., 1991). In a case series of people who received an intra-articular steroid injection to the knee with 40 mg Triamcinolone acetonide, flushing occurred in 40% of the 130 consecutive patients (Pattrick & Doherty, 1987). The inconsistent data may reflect under-reporting, different injection sites, variations in medicine and dose, co-morbidites, disgnosis, and study methodology.

Systemic adverse drug reaction/side effect	Drug/dose	Region of injection/ condition	Incidence	Study type (reference)	Summary of findings
Hypersensitivity reactions	Methylprednisolone/80 mg	Knee/Achilles tendon/hand and wrist	Three case studies	Case study (Brandt et al., 2017)	Immediate and uncommon hypersensitivity reactions (HSR) including hives, urticaria, angioedema, and anaphylaxis are reported side effects following CSI. No single corticosteroid molecule structure has been identified as the exact cause, but it is likely the corticosteroid molecule combined with serum, tissue proteins, or enzymes forms an immunogenic steroid-protein-enzyme conjugate acting as the hapten against which the immunoglobin response is directed (Habib, 2009). Although rare there have been well-documented cases of hypersensitivity reactions to steroids where reactions to excipients such as parabens, metabisulfites, and anaesthetics were excluded (Karsh & Yang, 2003). HSR occurred several hr after an intra-articular injection of prednisolone acetate (Comaish, 1969) and a case was recorded of anaphylactic reaction after injection with triamcinolone (Karsh & Yang, 2003). Similarly, a sudden onset of sneezing, angioedema, tachycardia, and marked hypotension reaction was attributable to methylprednisolone after exclusion of other constituents (Mace et al., 1997). The medical records of patients with suspected immediate HSR over a 9-year period were analysed and 64 patients underwent investigations for suspected type I HSR post-injection. True immediate HSR were found in only 14% (n = 9) of patients via positive skin tests or drug provocation tests. Most confirmed cases were allergic to the inert substance used to bulk up or dilute a drug (Li et al., 2018) known as an excipient. Three patients injected with depomedrone who subsequently developed allergic reactions were allergic to the excipient macrogol (Brandt et al., 2017).
Neuropsychiatric symptoms	Methylprednisolone/80 mg	Hip osteoarthritis	1–60%	Case study (Fischer & Kim, 2019)	CS have been associated with neuropsychiatric symptoms that may manifest as mood elevation, insomnia, psychosis, delusions, anger, paranoia, depression, mania, delirium, confusion, disorientation, or hallucinations (Fischer & Kim, 2019). Symptoms are more common with higher dose oral medication but have been reported after a single transforaminal epidural steroid injection (Fischer & Kim, 2019) and after a single injection of 5 mg of dexamethasone and 0.25% of bupivacaine for genitofemoral neuralgia (Janes et al., 2019). Following CSI for musculoskeletal conditions, auditory and visual hallucinations, confusion and poor judgement, anger, agitation, paranoia, hostility, excitability, euphoria, and insomnia have been reported as have excessive spending and grandiose thoughts (Janes et al., 2019). Symptoms have been reported after injections of both methylprednisolone and triamcinolone with onset ranging from the day after the injection(s) to seven days post injection and resolution ranging from 72 hr to 10 days after onset (Fischer & Kim, 2019). Neuropsychiatric symptoms following systemic corticosteroid therapy have a reported prevalence of < 1% to 60%. The percentage of severe psychotic disturbances following intra-articular and soft tissue injections are uncertain, but the available literature would suggest they are rare. There may be a higher incidence in people with a history of neuropsychiatric disorders but there is some uncertainty surrounding this (Fischer & Kim, 2019). There appears to be a higher prevalence of neuropsychiatric disorders with higher doses of corticosteroid and a daily dose exceeding 40 mg prednisolone (Fischer & Kim, 2019). If applied to injection therapy, then single-dose procedures of 40 mg prednisolone, 32.5 mg methylprednisolone or triamcinolone and 6 mg dexamethasone should be considered (Fischer & Kim, 2019).

Note: AI = adrenal insufficiency; BGL = blood glucose levels; CS = corticosteroid; CSI = corticosteroid injections; HSR = hypersensitivity reactions

Table 3

Recommendations for Future Research

Recommendations
Cartilage thinning
Do CSIs lead to cartilage thinning?
If yes, at what doses and volumes, frequency of injections, which joints are more and less commonly affected, does the addition of anaesthetic magnify, decrease, or not change the effect of CS on cartilage thinning?
Does this occur in all joints, or are some more vulnerable than others?
If this does occur, is it reversible?
Tendon degeneration and ruptures
Do CSIs lead to increased tendon degeneration and ruptures?
If yes, at what doses and volumes, frequency of injections, which tendons are more and less commonly affected, does the addition of anaesthetic magnify, decrease, or not change the effect of corticosteroids on tendon degeneration and ruptures?
Does this occur in all tendons, or are some more vulnerable than others?
If degeneration does occur, is it reversible?
Does CSI lead to an increase in surgery, and, if yes, is the effect influenced by the addition of anaesthetic, and are some tendons more vulnerable than others?
Joint infection
Should blood tests be conducted routinely in all, some, or no people, before joint injections to reduce the risk of unmasking a subclinical infection?
Glaucoma
Should tests be conducted routinely in all, some, or no people, before CSI to determine if closed angle glaucoma is present?
Subcutaneous fat atrophy and hypopigmentation
Should sustained pressure be maintained for a specific duration to reduce the risk of this occurring?
Should superficial structures more at risk be injected under ultrasound guidance?

Note. CSI = corticosteorid injection.

Table 4

Information to Support Shared Decision Making Prior to Considering a Corticosteroid Injection for Rotator Cuff-related Shoulder Pain

	Information
1.	CSIs for rotator cuff-related shoulder pain appear to have a small and transient benefit from 4–8 weeks.
2.	After 8 weeks CSIs have same benefit as anaesthetic-only injections.
3.	There is no evidence that CSIs have greater benefit than anaesthetic-only injections in the medium to long term.
4.	Numbers needed to treat = 5 and benefit when pain reduced may only be mild.
5.	When they help, there is uncertainty as to why they reduce symptoms – reasons include natural improvement, placebo, and therapeutic effect of the medication.
6.	Corticosteroid and anaesthetic injections theoretically may accelerate tendon and cartilage degeneration.
7.	If you have had surgery a CSI may increase the risk of you requiring additional surgery.
8.	CSIs are not a quick or guaranteed fix, and their use needs to be kept to minimum.
9.	You should only consider a CSI if the pain is significantly impairing your sleep and daily function.
10.	Multiple CSIs are no more beneficial than a single injection.
11.	All medicines are associated with side effects and adverse effects, and you must be informed of these.
12.	CSIs are more likely to be associated with negative effects in certain health conditions. The actual risks are often not known, but people considering CSI need to be made aware of these.
13.	Encourage the question "Is there another management option, including wait and watch?"

Note. CSI = corticosteroid injection. Publications from which this information has been sourced include Cook et al. (2018), Cook and Lewis (2019), Hoffman et al. (2020), Hopewell et al. (2021), Mohamadi et al. (2017), and Traven et al. (2018).

DISCLOSURES

There are no conflicts of interest that may be perceived to interfere with or bias this study. The authors affirm that we have no financial affiliation (including research funding) or involvement with any commercial organisation that has a direct financial interest in any matter included in this manuscript.

PERMISSIONS

Christine Bilsborough Smith and Jeremy Lewis have given permission for the use of Figure 1. Ethical approval was not required.

CONTRIBUTIONS OF AUTHORS

Conceptualisation and methodology, CBS, and JL; formal analysis, investigation and data curation, CBS, DB, RB, BD, RM, and JL; writing – original draft preparation, CBS, and JL; writing – review & editing, CBS, DB, RB, MC, RC, BD, RM, and JL.

The authors included two UK consultant physiotherapists (CBS, JL) who both perform ultrasound guided musculoskeletal injections and one (JL) who is an independent non-medical prescriber. Two UK specialist advanced practice physiotherapists (DB, RM) who are both independent non-medical prescribers and perform ultrasound guided injections. BD is a UK consultant orthopaedic surgeon and academic, and RB is a UK consultant musculoskeletal radiologist.

Figure 1

Decision-making Tool for Corticosteroid Injections For Adult Musculoskeletal Conditions

Decision making tool for corticosteroid injections for adult musculoskeletal conditions

NB: This does not include considerations for anaesthetics

Step one: Assessment

Conduct a full patient interview and physical examination

This will facilitate an understanding of the clinical presentation, and progression of the condition. It will enable risks or contraindications for injection therapy to be identified. It will assist in understanding the patient's values, beliefs, and aspirations around injection therapy.

Step two: Screening

Contraindications	Tick if applies
Feeling unwell – Current infection	☐
Taking antibiotics	☐
Aged under 18 years	☐
Currently on steroid management	☐
Site of prosthesis	☐
Pregnant/possibly pregnant/breastfeeding	☐
Recent trauma to intended site of injection	☐
Follow pre- and post-vaccination guidelines	☐
Immunocompromised (e.g., cancer HIV, TB)	☐
Planned surgery in next 3 months	☐

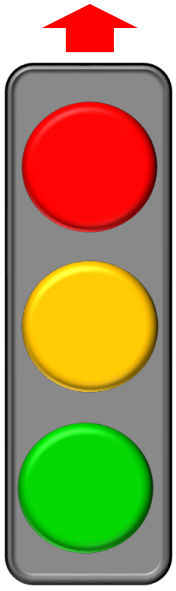
Any box ticked

No box ticked

Precautions	Tick if applies
Diabetes (Type 1/poorly controlled)	☐
Epilepsy	☐
Hypertension (assess if taking beta blockers)	☐
Currently on steroid treatment	☐
Adrenal insufficiency/Cushing's syndrome	☐
Bradycardia > 50 bpm	☐
Kidney function compromise	☐
Liver function compromise	☐
Myasthenia gravis	☐
Neurological conditions	☐
Glaucoma (closed angle)	☐
Follow pre- and post-vaccination guidelines	☐
Recent abdominal surgery	☐
≥3 steroid injections in past 12 months	☐

Any box ticked

No box ticked



DO NOT PROCEED

Consider other options such as physiotherapy management, activity modification, other pharmacological intervention, surgical opinion

SEEK GUIDANCE

If there is any degree of uncertainty, speak with the GP, consultant, rheumatologist, or other specialist. For example, contacting the patients ophthalmologist to determine if safe to proceed in the presence of closed angle glaucoma. The level of experience and degree of confidence a clinician has, may determine if and from whom guidance is sought. Following guidance, a decision to proceed or not proceed will be made.

PROCEED WITH INJECTION

Procced with the injection once a shared decision-making process has been completed and the patient is cognizant of the intended benefits, timeframes, harms, including side effects and potential adverse events

Step three: Shared decision making

Shared decision making

Shared decision making is at the centre of providing safe patient care. Discuss the risks and benefits where evidence is available. Ensure the patient is aware of alternatives including no treatment, no injection, and other management options. Patients should be aware of the side effects, adverse effects, and serious adverse effects of corticosteroid injections, as well as the limitations of the procedures which in some cases may be substantial.

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