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THERAPY IN PRACTICE

Reducing clinical risks associated with the pharmacological treatment of acute gout attacks

Sanja Mirkov[1]

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Abstract Pharmacological treatment of acute gout attacks includes colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids. The choice of treatment depends on comorbidities and drug–drug interactions, requiring careful patient screening. As the use of these medications is associated with increased clinical risks, they should be used at the lowest effective dose for the shortest period of time alongside ongoing urate-lowering therapy to prevent gout attacks and to minimise their use. This article discusses the major clinical risks associated with colchicine, NSAIDs and glucocorticoids and risk minimisation strategies for their safe and effective use in this patient population.

Introduction

Gout (urate crystal arthritis) affects 0.9–2.5% of the general population [1, 2] and is increasing in prevalence. A high prevalence of the disease is seen in specific groups, such as elderly men (affects > 10%) and patients with chronic kidney disease (CKD) [24%] [3]. Gout causes significant pain and functional impairment, and is associated with social stigma due to belief that is self-inflicted disease of lifestyle excess for which dietary solutions are most important and effective.

Gout is associated with a number of serious comorbidities, such as hypertension, diabetes mellitus, ischaemic heart disease, kidney disease and obesity. Certain drugs used to treat these conditions raise serum urate levels (thiazide, loop diuretics), impair the actions of urate-lowering drugs (frusemide) or lower serum urate levels (losartan) [1].

The risk of developing gout is twice as high in patients with CKD as in individuals without CKD at baseline [hazard ratio (HR) 2.09; 95% CI 1.41–3.08] [4]. In patients with CKD, gout is relatively hard to treat due to contraindications to medications and a lack of drug efficacy [3].

The management of gout is often suboptimal [2, 5, 6]. Most people with gout are not treated with effective long-term urate-lowering therapy (e.g. allopurinol, febuxostat, probenecid or benzbromarone) [5] and are subsequently exposed repeatedly to the risks of anti-inflammatory medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and glucocorticoids used to treat acute gout attacks [7, 8]. In addition, improvements are required in patient assessment, regular testing of serum uric acid (< 0.36 or < 0.3 mmol/L if tophi are present) and provision of patient education on the importance of adherence with urate-lowering therapy and benefits of lifestyle modifications [6] to reduce the incidence of acute gout flares and subsequent need for therapy of acute attacks. This article addresses the major risks and risk minimisation strategies for pharmacological treatment of acute gout flares.

Pharmacological treatment of acute gout attacks

Recommended first-line options for treatment of acute gout flare or prophylaxis of gout attack during initiation of urate-lowering therapy are colchicine and/or an NSAID,

✉ Sanja Mirkov
sanja.mirkov@otago.ac.nz

[1] School of Pharmacy, University of Otago, Dunedin, New Zealand

oral or intramuscular corticosteroids or articular aspiration and injection of corticosteroids [2]. Interleukin (IL-1) blockers are recommended in patients in whom colchicine, NSAIDs and glucocorticoids are contraindicated [2]. Screening for comorbidities and drug–drug interactions is essential as this dictates the choice of treatment. For example, colchicine and NSAIDs are contraindicated in patients with severe renal failure, colchicine is contraindicated with concomitant administration of strong CYP3A4 or P-glycoprotein (P-gp) inhibitors and IL-1 blockers are contraindicated in current infection. The first-line pharmacological options for treatment of acute gout flares are outlined in Table 1.

Reducing the clinical risks of colchicine

The dosage of colchicine used to treat acute gout attacks varies between countries [13, 14]. A randomised controlled trial demonstrated that low-dose colchicine (1 mg followed by 0.5 mg 1 h later) was effective when prescribed within 12 h of onset of an acute attack, with a low incidence of gastrointestinal (GI) adverse effects [2, 15]. A higher dose (1 mg followed by 0.5 mg every h for 6 h) was associated with the increased risk of GI toxicity without additional clinical benefit [8].

Colchicine has a narrow therapeutic index and is associated with high risks of toxicity and death (see Table 2). Acute overdose exceeding 0.5 mg/kg is usually fatal. Fatalities have been reported with doses as low as 6 mg [14, 16]. Patients who are elderly, have impaired liver or renal function, and weigh < 50 kg have an increased risk of colchicine-induced toxicity [13].

Colchicine-induced harm is due to its inhibitory effect on the cell mitotic spindle. Colchicine binds to tubulin during mitosis, inhibits microtubule polymerisation and mitotic spindles formation. The cells cannot divide and this results in cell death. The anti-mitotic effects of colchicine affect all cell lines resulting in multi-organ toxicity [17].

Early symptoms of colchicine toxicity include GI symptoms (e.g. abdominal pain, diarrhoea, nausea, vomiting). These symptoms, particularly diarrhoea, can also occur with dosages within the therapeutic range. Delayed symptoms of toxicity [e.g. tachypnoea, electrolyte disorders (hypocalcaemia, hypophosphataemia), hypovolaemia, haematological effects (leukopaenia, thrombocytopaenia), seizure, shock, coagulopathy, cardiac dysrhythmias, respiratory, renal failure, liver damage and rhabdomyolysis] usually occur 24 h–7 days after ingestion. The cause of death is usually progressive multiple organ failure. There is no specific antidote for colchicine [14, 18].

Reducing the clinical risks of nonsteroidal anti-inflammatory drugs (NSAIDs)

For treatment of acute gout, NSAIDs that inhibit cyclo-oxygenase (COX)-1 and -2 enzymes provide rapid relief from pain and inflammation [2]. However, the harm associated with higher doses and prolonged use of both types of NSAIDs is a major safety problem [25]. NSAIDs are among the top four drug classes responsible for preventable drug-related hospital admissions [26, 27]. According to a systematic review, NSAIDs were identified as the third leading cause of preventable hospital admissions, with 11% of preventable hospital admission being attributed to their use [26]. Likewise, a prospective observational study of 1225 hospital admissions revealed that NSAIDs were implicated in 12% of the cases requiring hospitalisation [27].

NSAID-induced cardiovascular disease

The clinical risks associated with the different NSAIDs are determined by their ability to inhibit COX-1 and -2. Selective COX-2 inhibitors were initially developed with the intention of reducing GI adverse effects. However, it was later discovered that COX-2 activity inhibits platelet aggregation, promoting thrombosis and atherothrombotic events, such as myocardial infarction (MI) [28, 29].

Data on the relative risk (RR) of cardiovascular (CV) events with individual NSAIDs were derived from meta-analyses of randomised trials and controlled observational studies. Rofecoxib, diclofenac and etoricoxib ranked consistently highest in terms of CV risk relative to nonuse. Naproxen was associated with the lowest risk while diclofenac demonstrated the highest CV risk [30]. In addition, NSAIDs with longer half-lives (e.g. naproxen) are more suited for the treatment of chronic conditions [28]. A recent meta-analysis revealed that all NSAIDs, including naproxen, were associated with an increased risk of acute MI [OR (95% CI) for celecoxib 1.24 (0.91–1.82), ibuprofen 1.48 (1.00–2.26), diclofenac 1.5 (1.06–2.04), naproxen 1.53 (1.07–2.33) and rofecoxib 1.58 (1.07–2.17)] [31]. The risk was highest during the first month of NSAID use and with higher dosages [31]. The evidence suggests advising caution against both short-term and long-term use of NSAIDs and selective COX-2 inhibitors in patients with a high risk of CV disease.

A non-NSAID agent, paracetamol (acetaminophen), is the preferred pain relief in patients with high CV risk; however, it is not suitable in the treatment of acute gout attacks [25]. If required, a stepwise approach is suggested, beginning with an NSAID with the lowest associated CV risk (e.g. naproxen) and moving to the agents with higher risk.

Table 1 Medications used as first-line treatment for acute gout attacks [9–13]

	NSAIDs	Colchicine	Glucocorticoids
Mechanism of action	Inhibits prostaglandin synthesis	Inhibits a glycoprotein produced during the phagocytosis of urate crystals, inhibits urate crystal deposition	Inhibits prostaglandin synthesis
Major contraindications	Cl_{CR} < 30 mL/min Previous NSAID-induced kidney injury, liver injury or GI bleeding Severe cardiac failure, active GI ulceration or bleeding History of recurrent GI bleeding Hypersensitivity to aspirin or other NSAIDs	Cl_{CR} < 10 mL/min, severe liver impairment or cardiac disease Pts with mild or moderate renal impairment taking a P-gp or strong CYP3A4 inhibitor Pts with blood dyscrasias Pregnancy, children, lactation Hypersensitivity to colchicine	Systemic infections unless specific anti-infective therapy is given Live virus immunisation Pancreatitis Hypersensitivity to prednisone
Prophylactic dosage[a]	Low (e.g. naproxen 250 mg twice daily) + proton pump inhibitor	Cl_{CR} > 50 mL/min: 0.5 mg twice daily Cl_{CR} < 50 mL/min: 0.5 mg once daily	Low (e.g. ≤ 10 mg prednisolone once daily)
Dosage for treatment of acute attack	Naproxen (as an example): initial dose 750 mg; maintenance: 250 mg every 8 h until attack subsides Adjust the dose in pts with renal impairment	1 mg as soon as possible, then 0.5 mg 1 h later, maximum 1.5 mg per course Do not repeat the course within 3 days	Prednisolone 15–20 mg (up to 35 mg) daily × 3–5 days (best taken prior to 9am)
Monitoring	Renal and liver function	Signs of abdominal pain, diarrhoea, nausea, vomiting Full blood count, renal and liver function	Signs of infection, blood glucose
Significant drug interactions	Anticoagulants Methotrexate Calcineurin inhibitors (ciclosporin, tacrolimus) Lithium	P-gp or strong CYP3A4 inhibitors (e.g. calcium channel blockers, calcineurin inhibitors, statins, azole antifungals, digoxin, dabigatran, macrolide antibiotics, protease inhibitors, antineoplastics)	CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin), CYP3A4 inhibitors, hypoglycaemic agents, NSAIDs, digoxin
Serious adverse effects	GI haemorrhage, acute kidney injury, congestive heart failure	Diarrhoea, myelosuppression	Osteoporosis, hyperglycaemia/worsening of diabetes control, GI bleeding, congestive heart failure, infection, Cushing syndrome, increased IOP, psychosis

Cl_{CR} creatinine clearance, *CYP* cytochrome P450, *GI* gastrointestinal, *IOP* intra-ocular pressure, *NSAIDs* nonsteroidal anti-inflammatory drugs, *P-gp* P-glycoprotein inhibitors, *pts* patients

[a]When starting urate-lowering therapy, concomitant prophylaxis should be provided for a minimum of 6 months

When initiating any NSAID in a patient with high CV risk, it is important to monitor blood pressure (BP). Concurrent use of NSAIDs with antihypertensive medications has been associated with a decrease in the BP-lowering effects of the antihypertensive. NSAIDs increase systolic BP by an average of 2–3 mmHg and double the risk of hospital admission due to heart failure [25, 28].

NSAID-induced kidney disease

NSAID-induced acute kidney injury (AKI) accounts for up to 15.6% of cases of drug-induced renal failure [32]. Both classes of NSAIDs cause afferent arteriolar vasocontraction by inhibiting prostaglandin synthesis [25, 33, 34].

The mechanisms of NSAID-induced kidney injury include haemodynamically mediated AKI due to ischaemic acute tubular necrosis (ATN); immune-mediated AKI due to glomerular disease or acute allergic interstitial nephritis (AIN); and chronic interstitial nephritis and papillary necrosis [35, 36]. ATN, the most common type, is due to decreased synthesis of renal prostaglandins, which can lead to reduced blood flow and reduced glomerular filtration in susceptible individuals. NSAID-induced haemodynamic renal failure is reversible with appropriate management;

Table 2 Risks and recommended risk minimisation strategies for the safe use of colchicine

Risks associated with colchicine
Overdose caused by exceeding the maximum daily and cumulative dosages due to incorrect prescribing or labelling
Overdose caused by prescribing colchicine to pts who are elderly, have impaired hepatic or renal function, or weigh < 50 kg in doses exceeding the maximum dosage of 1 mg/day and cumulative dose of 3 mg/4 days
Overdose caused by prescribing colchicine together with strong inhibitors of P-gp or CYP3A4 enzymes (e.g. calcium channel blockers, calcineurin inhibitors, statins, azole antifungals, digoxin, dabigatran, macrolide antibiotics, protease inhibitors, antineoplastics) leading to colchicine accumulation
Overdose caused by taking excessive no. of tablets due to pt's lack of knowledge about colchicine, including maximum daily and cumulative dose, and not understanding that colchicine is not used for pain relief
Not recognising early signs of colchicine toxicity (e.g. diarrhoea, abdominal pain), resulting from failure to educate pts about early signs of colchicine toxicity that require drug discontinuation
Poisoning due to not keeping colchicine out of reach of children in a child-proof container
Risk management: preventing adverse drug reactions and drug–drug interactions
Check pt's medical history for contraindications and precautions
Obtain best possible medication history including recent medication changes and use of over-the-counter medications
Check for adverse drug reactions and potential drug–drug interactions
Risk management: collaboration between physicians and pharmacists
Ensure urate-lowering therapy is prescribed, as preventative treatment to ↓ flare frequency and the need for acute treatment with colchicine. thereby ↓ the risk of toxicity [19]
Ensure the prescription specifies the maximum daily and cumulative dose of colchicine [20]
Use lower doses of colchicine in pts at ↑ risk of toxicity
Prescribe small numbers of tablets (e.g. 12 tablets of 0.5 mg colchicine for acute attack, 6 tablets for older people, or 30 tablets with repeats sufficient for a 3-month supply) [21]
Monitor blood counts, renal and liver function
Standardise documentation for follow-up of problematic prescriptions [22]
Risk management: pharmacist process for high-risk medication
Prepare medication label and updated medication list outlining the appropriate pt-centred description [23] of colchicine regimen
Provide clear dosage advice on maximum daily and cumulative doses on the prescription label (e.g. 0.6-mg tablets in USA: "For gout attack take 2 tablets as soon as possible, then 1 tablet 1 h later. Do not repeat the course within 3 days"; 0.5-mg tablets in New Zealand for healthy adults: "For gout attack take 2 tablets as soon as possible. Wait for at least 6 h before taking 1 tablet again. Do not take more than 5 tablets in 24 h. Do not take more than 3 tablets in 24 h on 3 subsequent days. Do not take more than 12 tablets over 4 days. Do not repeat the course within 3 days"; pts who are elderly, have renal or hepatic impairment, or weigh < 50 kg: "For gout attack take 2 tablets as soon as possible on the first day. On the following day, if necessary take 1 tablet. Wait at least 12 h before taking again. Do not take more than 2 tablets in 24 h. Do not take more than 6 tablets over 4 days. Do not repeat the course within 3 days"
Create a default dosage regimen for colchicine for acute gout attack in the electronic system [24]
Dispense colchicine in a child-proof container
Perform independent double checks during dispensing process [22]
Scan bar codes to ensure correct selection of medication during dispensing process [22]
Risk management: engagement between pt and provider
Tailor advice to the pt's level of health literacy; use 'show and tell' and 'teach back' techniques [22]
Educate the pt/carer about medicating at the first warning symptoms [2], and on maximum daily and cumulative doses
Explain that taking extra doses is dangerous
Colchicine prophylaxis must be stopped before treatment of acute attack begins
Warn pts of the symptoms of colchicine toxicity and advise them to immediately stop taking colchicine and see their doctor if following symptoms occur: abdominal pain, diarrhoea, nausea or vomiting, unusual bleeding or bruising, burning feeling in throat, stomach or on skin, muscle pain or weakness; or numbness or tingling in fingers or toes
Ensure pts are aware that colchicine is not an analgesic for general use and should not be used to manage pain due to gout
Explain the importance of taking urate-lowering therapy
Encourage pt to carry a medication list when interacting with healthcare professionals [22]
Advise pt to keep tablets away from reach of children
Advise pt to avoid eating grapefruit and drinking grapefruit juice when taking colchicine
Check that pts/caregivers understand

CYP cytochrome P450, *P-gp* P-glycoprotein, *pt(s)* patient(s), ↑ increase (s/d), ↓ decrease (s/d)

the relatively rare complications of interstitial nephritis and papillary necrosis are more often irreversible.

Patients who are elderly, have severe heart disease (congestive heart failure), severe liver disease (cirrhosis), nephrotic syndrome (low oncotic pressure), CKD or protracted dehydration (several days) have an increased risk of NSAID-induced kidney injury [33]. The triple-therapy combination of a diuretic plus an ACE inhibitor or angiotensin receptor blockers (ARBs) plus an NSAID was associated with an increased risk of AKI (rate ratio 1.31, 95% CI 1.12–1.53). The highest risk was observed in the first 30 days of use (rate ratio 1.82, 95% CI 1.35–2.46) [37].

NSAID-induced gastrointestinal bleeding

NSAID-induced GI bleeding is mediated by inhibition of COX-1, which is responsible for synthesis of the prostaglandins that inhibit acid secretion [38, 39]. Patients at risk are those aged > 65 years, with a history of peptic ulcer or GI bleeding, previous gastric irritation with NSAID use, taking multiple NSAIDs or COX-2 inhibitors, using high dosages of NSAIDs, taking NSAIDs for a prolonged time, taking medications which predispose to GI bleeding, consuming excessive alcohol or who are heavy smokers [25, 38, 39]. In addition, NSAIDs with a long half-life or a slow-release formulation are associated with an increased risk of upper GI bleeding [28].

A survey conducted among regular users of over-the-counter analgesics revealed that the proportion of responders who were aware of potential risks associated with NSAIDs increased from 25% in 2001 to 41.1% in 2009 and the proportion of responders who knew to consider GI conditions prior to NSAID use increased from 13% to 22% [40]. See Table 3 for risks and risk minimisation strategies for the safe use of NSAIDs.

Reducing the clinical risks of glucocorticoids

The risks and benefits of systemic glucocorticoids depend on the dosage (low vs medium and high dosage treatment) and cumulative dose [42]. Medium (prednisolone 15–20 mg/day) [10] to high dosages (30–35 mg/day) for 5 days are used to treat acute gout attacks [2, 10], whereas low doses (< 10 mg/day) for up to 6 months are used for gout prophylaxis when initiating urate-lowering therapy [10].

Glucocorticoids are suitable for patients with renal impairment or those taking CYP3A4 or P-gp inhibitors in whom NSAIDs and colchicine are contraindicated [2, 5]. The use of glucocorticoids should take into account the presence of GI disease and diabetes [5]. Oral prednisolone 35 mg/day for 5 days is equivalent to twice-daily naproxen 500 mg for 5 days for treating acute gout flares [43], and oral prednisolone demonstrated analgesic properties equivalent to those with indomethacin [44].

Systemic glucocorticoids, given orally or as an intra-articular or intramuscular injection, appeared safer than NSAIDs based on the results from a series of systematic reviews comparing efficacy and safety of glucocorticoids, NSAIDs and colchicine for treatment of acute gout; however, the evidence was insufficient to rank the treatment options [45]. Systemic glucocorticoids appeared safer than NSAIDs [45]. Likewise, safety data on low-dose glucocorticoids for treatment of rheumatoid arthritis also demonstrated that adverse effects were modest [46].

Major clinical risks associated with low-dose glucocorticoids include CV adverse effects [47], glucose intolerance, osteoporosis, increased risk of GI bleeding and increased susceptibility to infection [46].

Osteoporosis is the most common adverse effect associated with chronic use of low-dose glucocorticoid therapy; it is related to cumulative tissue exposure [42] and it is preventable [46]. Increase in fracture risk is rapid, with significant increases in risk of nonvertebral fracture becoming apparent within the first 3 months of treatment. All fracture risks declined toward baseline rapidly after cessation of oral corticosteroid treatment. Relative risk for hip fracture compared with control was 1.77 (95% CI 1.55–2.02) at daily doses of prednisone 2.5–7.5 mg, and 2.27 (95% CI 1.94–2.66) at doses of 7.5 mg or greater. The relative rates for vertebral fracture were 1.55 (95% CI 1.20–2.01), 2.59 (95% CI 2.16–3.10) and 5.18 (95% CI 4.25–6.31) for doses < 2.5, 2.5–7.5 and > 7.5 mg/day prednisone, respectively [46].

Glucocorticoid treatment is a risk factor for dyslipidaemia and atherosclerosis. A population-based cohort study among patients with rheumatoid arthritis revealed that glucocorticoid use was associated with a 68% increase in risk of MI (HR 1.68; 95% CI 1.14–2.47) [47]. The risk of MI was related to an immediate effect of the current daily dose (HR 1.14; 95% CI 1.05–1.24 per each 5 mg/day increase), duration of therapy (HR 1.14; 95% CI 1.00–1.29 per year of glucocorticoid use) and cumulative dose of glucocorticoids (HR 1.06; 95% CI 1.02–1.10 per gram accumulated in the past). In addition, current dose and cumulative use were independently associated with an increased risk of MI (10% per additional year on glucocorticoids and 13% per 5 mg/day increase) [47].

Glucose intolerance is dose dependent; however, patients taking low doses of oral glucocorticoids equivalent to prednisone 0.25–2.5 mg daily are at increased risk for initiation of hypoglycaemic medications (odds ratio 2.23; 95% CI 1.92–2.59) compared with non-users [48]. Glucocorticoid-related hyperglycaemia has been reported after

Table 3 Risks and recommended risk minimisation strategies for the safe use of NSAIDs

Cardiovascular risks associated with NSAIDs
Use, especially at high dosages (e.g. diclofenac 150 mg/day, ibuprofen 2.4 g/day, naproxen 1 g/day), can result in potentially fatal thrombotic events (heart attack and ischaemic stroke)
Loss of BP control in pts with pre-existing hypertension taking antihypertensives could lead to sodium and water retention, fluid overload, haemorrhagic stroke, worsening of cardiac function, and even death
Renal risks associated with NSAIDs
Erroneous prescribing in at-risk pts, not stopping treatment in pts with hypovolaemia due to acute illness (e.g. upper or lower respiratory tract infection, urinary tract infection, sepsis or GI illness) and prescribing NSAIDs in combination with an ACE inhibitor/ARB and diuretic (the triple whammy) or other nephrotoxic medications can lead to AKI
Erroneous prescribing in pts with a history of allergic reaction to an NSAID can result in immune-mediated AKI due to acute allergic interstitial nephritis
Prolonged use of high doses in pts at risk of NSAID-induced renal injury can result in chronic interstitial nephritis and renal papillary necrosis
GI bleeding risks associated with NSAIDs
Prescribing without contaminant GI protection in pts at ↑ risk of GI ulceration can lead to GI bleeding
Risk management: preventing adverse drug reactions and drug–drug interactions
Check pt's medical history for contraindications and precautions
Obtain best possible medication history, including recent medication changes and use of OTC medications and NSAIDs
Check for adverse drug reactions and previous NSAID-induced kidney injury or GI bleeding
Check for potential drug–drug interactions, including medications that ↑ the risk of nephrotoxicity (e.g. an ACE inhibitor/ARB + a diuretic, ciclosporin [34], tacrolimus [34]) or bleeding (e.g. corticosteroids, anticoagulants or selective serotonin reuptake inhibitors) [38], or medications that may be affected by NSAIDs (e.g. toxicity of lithium [33] and methotrexate [41] is ↑)
Risk management: collaboration between physicians and pharmacists
Ensure that the lowest effective dose of an NSAID is used for the shortest period of time
Review the need for long-term treatment
If possible, avoid prescribing slow-release formulation due to the ↑ risk of GI bleeding [28]
Ensure a PPI or histamine H_2 antagonist is co-prescribed in pts with ↑ risk of GI bleeding [25, 39]
Monitor blood pressure, weight, renal and liver function, serum potassium, haemoglobin levels for month 1 of treatment and periodically thereafter
Standardise documentation for follow-up of problematic prescriptions [22]
Risk management: pharmacist process for high-risk medication
Scan bar codes to ensure correct selection of medication during dispensing process [22]
Prepare updated medication list
Risk management: engagement between pt and provider
Advise pts to take the lowest possible dose of NSAID for the shortest period of time
Advise elderly pts and those with diabetes, renal, cardiac or liver disease not to self-medicate with NSAIDs
Advise pts taking an ACE inhibitor/ARB + a diuretic not to self-medicate with NSAIDs
Advise pts to stop taking NSAIDs if they develop an acute illness, especially if they become dehydrated (e.g. from vomiting or moderate to severe diarrhoea, poor fluid intake, fevers, sweats and shaking) and restart NSAID once they are well (after 24–48 h of eating and drinking normally); advice pts to maintain fluid and electrolyte balance
Advise pts to take NSAIDs with food
Advise pts to discontinue the NSAID and contact a health professional if they experience shortness of breath, fatigue, confusion, nausea, ↓ urine output, ankle/leg swelling, ↑ in BP, chest pain, trouble breathing, sudden weakness in one part or side of the body, sudden slurred speech, stomach discomfort, heart burn or black stools, or experience systemic hypersensitivity including fever, arthralgia and a pruritic erythematous rash
Encourage pts to carry a medication list when interacting with healthcare professionals [22]

AKI acute kidney injury, *ARB* angiotensin receptor blocker, *BP* blood pressure, *GI* gastrointestinal, *OTC* over-the-counter, *PPI* proton pump inhibitor, *pt(s)* patient(s), ↑ increase(s/d), ↓ decrease (s/d)

Table 4 Risks and recommended risk minimisation strategies for safe use of glucocorticoids (GCs)
Risk of bone fractures associated with long-term use of GCs
Caused by osteoporosis in pts who were taking GCs long term without osteoporosis prophylaxis/treatment
Cardiovascular risk associated with GCs
Use of GCs can result in thrombotic events (heart attack) caused by GC-induced dyslipidaemia and atherosclerosis
Loss of BP control could lead to sodium and water retention, fluid overload, haemorrhagic stroke, worsening of cardiac function
Hyperglycaemia and worsening of glycaemic control in patients with DM associated with GCs
GI bleeding risk associated with GCs
Prescribing without concomitant GI protection in pts at ↑ risk of GI ulceration can lead to GI bleeding
Infection risk with GCs
↑ susceptibility to viral, bacterial, fungal and parasitic infections associated with GCs
Risk management: preventing adverse drug reactions and drug–drug interactions
Check pt's medical history for contraindications and precautions
Obtain best possible medication history and assess cumulative dose of GCs
Check for adverse drug reaction and previous GC-induced adverse drug reactions
Check for potential drug–drug interactions including medications that ↓ the systemic GC concentration (e.g. aluminium/magnesium hydroxide, phenobarbital, phenytoin, rifampicin, St John's wort) or ↑ the systemic GC concentration (e.g. macrolide antibiotics, azole antifungal agents, indomethacin) or ↑ the risk of GI bleeding (e.g. aspirin, anticoagulants, NSAIDs or selective serotonin reuptake inhibitors) or ↑ risk of infection [live vaccines (contraindicated)] or medications that may be affected by GCs (e.g. digoxin toxicity is ↑ due to GC-induced hypokalaemia, effect of glycose-lowering therapy is ↓)
Risk management: collaboration between physician and pharmacists
Ensure that the lowest effective dose of GCs is used for the shortest period time [51]
Ensure osteoporosis prophylaxis or treatment (e.g. bisphosphonates with vitamin D) has been prescribed if indicated for patients at increased risk of fracture (age > 65 years, previous fragility fracture) [52]
Ensure a proton pump inhibitor or histamine H_2 antagonist is co-prescribed in pts with ↑ risk of GI bleeding
Monitor BP, weight, serum glucose, sodium, potassium and calcium, and haemoglobin levels for the first month of treatment and periodically thereafter
Have a standardised document for follow up of problematic prescriptions [22]
Risk management: pharmacist process for high-risk medication
Scan bar codes to ensure correct selection of medication during dispensing process [22]
Prepare medication label and updated medication list outlining appropriate patient-centred description of GCs regimen [e.g. "For gout attack take X tablets (Y mg) orally in the morning (at 8 a.m.) for 5 days then stop"] [23, 42]
Risk management: engagement between pt and provider
Advise pts not to stop prophylactic treatment abruptly
Advise pts to take GCs with food
Advise pts taking GCs not to self-medicate with NSAIDs due to ↑ risk of GI bleeding and cardiovascular risk
Advise pts with DM that dose adjustment of antidiabetic drugs may be required due to GC-induced worsening of glycaemic control
Advise pts to contact a health professional if they experience ↑ in BP, weight gain, swelling, chest pain, trouble breathing or urinating more often, feeling thirsty or having muscle or bone aches and pains or stomach discomfort, heart burn, black stools or fever, chills, sweats, fatigue, sore throat, cough, shortness of breath, muscle aches, burning or pain with urination, diarrhoea, pus or fluid leaks out of the cut, mood or behavioural changes or changes in vision
Encourage patient to carry a medication list when interacting with healthcare professionals [22] and mention therapy with GCs when receiving treatment for any illness or injury

BP blood pressure, *DM* diabetes mellitus, *GI* gastrointestinal, *pt(s)* patient(s), ↑ increase(s/d), ↓ decrease (s/d)

intra-articular glucocorticoid therapy [49]. New-onset diabetes in individuals at risk for developing diabetes and worsening of glycaemic control in diabetic patents are recognised adverse effects.

Glucocorticoid therapy has been associated with increased risk of upper-GI bleeding or perforation [50]. The RR of upper GI complications is 1.8 (95% CI 1.3–2.4) for users of glucocorticoids compared with non-users and the risk is dose related; low to medium dose RR 1.5 (95% CI 1.1–2.1) and high dose RR 2.9 (95% CI 1.2–7.3). Concomitant use of both glucocorticoids and NSAIDs is associated with increased risk of GI bleeding [RR 8.5 (95% CI 3.9–18.9)] compared with non-use of either drug [50].

Low-dose prednisone up to 10 mg/day was not associated with increased incidence of infections [46]. However, in patients treated with glucocorticoids, physicians should anticipate the risk of infections as glucocorticoids may blunt the classic clinical features and delay the diagnosis. Severely immunocompromised patients require prophylaxis for *Pneumocystis carinii* infection and may need to be screened for latent tuberculosis, or prescribed prophylactic chemotherapy. See Table 4 for risks and risk minimisation strategies for safe use of glucocorticoids.

Take-home message

General Ensure the patient has been prescribed urate-lowering therapy to prevent gout attacks; educate patients on the importance of adherence with urate-lowering therapy and benefits of lifestyle changes; treat acute gout flares based on the individual's comorbidities and drug's safety profile; educate patients to self-medicate at the first warning symptoms of gout attack.

Colchicine Specify maximum daily and cumulative dosages; use lower doses in at-risk patients; avoid serious interactions with strong CYP3A4 and P-gp inhibitors; dispense in small packs in a child-proof container; provide patient education on maximum daily and cumulative dosages, and the symptoms of toxicity, and check that they understand.

NSAIDs Avoid use in patients at risk of NSAID-induced harm, avoid the triple whammy of a combination of an ACE inhibitors/ARB plus a diuretic + an NSAID; educate patients to use the lowest effective dose for the shortest period of time; advise at-risk patients not to self-medicate with NSAIDs.

Glucocorticoids Prescribe oral glucocorticoids at the lowest effective dose for the shortest period of time; ensure osteoporosis prophylaxis/treatment is prescribed when indicated; educate patients to not stop long-term treatment abruptly or to self-medicate with NSAIDs; advise patients with diabetes that dose adjustment of antidiabetic drugs may be required.

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