# Risk of Systemic Adverse Effects from Topical and Oral Corticosteroids: Time for a Paradigm Shift?

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## DISCLOSURES

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## INTRODUCTION

- Corticosteroids (CS) are among the most frequently prescribed drugs in US outpatient care[1]
- Multiple systemic, inhaled, intranasal, and topical CS products rank among the most commonly dispensed medications across specialties, including dermatology, allergy, immunology, rheumatology, gastroenterology, and primary care
  - In 2023 alone, >15 million topical CS prescriptions for any indication were filled in the US[1]
  - Oral CS are widely prescribed in the US by multiple clinical specialties,[2,3] often in high doses (≥20 mg prednisone equivalent/day) and for prolonged durations (≥3 months)[4,5]
- A growing body of clinical literature shows that this widespread use is accompanied by increased risk for dose-dependent and cumulative systemic AEs[6-9]
  - AEs associated with topical CS use have traditionally been considered to be limited to the skin; however, growing evidence suggests that systemic absorption of topically applied CS may lead to a variety of systemic AEs[10-11]
  - The AE profile of oral CS is well-characterized for high-dose and/or long-term use,[12,13] but lower doses and shorter courses of treatment are increasingly recognized as associated with safety risks[3,14]

## OBJECTIVE

- A targeted literature search was performed to better understand the safety risks associated with topical and oral CS use

## METHODS

- Relevant articles were identified via a PubMed search
  - Limits: English-language publications, clinical studies, meta-analyses, published 2010–2025
  - Search terms included but were not limited to: topical corticosteroids, corticosteroids, glucocorticoids, dose-response, threshold dose, cumulative dose, potency, duration, frequency, population-based, cohort, registry, claims database, observational study, case-control study, cohort study, and specific adverse events (eg, T2D, osteoporotic fracture, adrenal suppression)
  - Reference lists from selected articles were reviewed for additional sources
- A total of 9 papers for topical CS and 30 papers for oral CS were identified
  - Papers were screened, and those that reported risks of TCS (N=8) and oral CS (N=29) use were summarized

## RESULTS

### TCS Literature Review

- AEs attributed to TCS have, until relatively recently, been considered to be limited to the skin (ie, skin atrophy, striae)[15,16]
  - Data informing the risks of TCS use are limited by small studies that evaluated narrow dose ranges and short durations of exposure,[17] or did not rigorously assess or report systemic AEs (ie, T2D, HPA axis suppression) in a rigorous fashion[18]
- Results of cohort and case-control studies show that prolonged use of TCS (especially high potency TCS) confers a modest, but clinically meaningful, risk of HPA axis suppression, T2D, osteoporosis, and osteoporotic fractures[10,11,19,20]
- Increased risk is present even with short-term (≤60 days) use[21]
  - Particular attention should be paid to risks associated with TCS use during pregnancy[22,23]
- Use of ≥50 g/week of very high-potency topical CS for ≥1 month was identified as a threshold for HPA axis suppression in a study of patients with PsO[20]
  - Some doses of potent TCS may exceed this threshold for HPA axis suppression[16,24] (**Figure**)

### Oral CS Literature Review

- Short-term oral CS use is common overall and is often used as "bridge therapy" or to quell disease flares[25]
  - A national claims database study found that 21% of 1,548,945 US adults (excluding those with asthma, COPD, cancer, or an inflammatory disease) received ≥1 outpatient prescription for a short-term (<30 days) oral CS over a 3 year period[3]
- Contrary to typically held beliefs, short courses of oral CS are not without risks, which include CV effects, GI bleeding, sepsis, and fracture[3,26]
- The daily CS dose–response relationship is well documented[14,27-44] as well as the relationship with current/recent exposure vs past use[39-42,45]
- Doses ≤7.5 or ≤10 mg/day have been suggested as a threshold for oral CS-related risk,[27,35,46-51] but many studies have evaluated cumulative dose[35-45,52-56] and duration of exposure[35,55,57] as more relevant markers of risk
  - Even short-term (≤6 months) oral CS use and cumulative doses <1 g have been linked to increased risk of CVD,[3,35,37,54,56] T2D,[39,41,54,56] osteoporotic fractures,[3,42,43,45,56,57] and other systemic AEs[3,44,54-56]
  - Serious AEs (ie, renal impairment, CV/cerebrovascular disease) are associated with lifetime cumulative doses of CS as low as 0.5 to <1 g (ie, 4 lifetime short courses of oral CS)[56]

**Safety Risks With Topical CS Use Reported in Population-Based Studies (unless otherwise noted)**

| | | | TCS use *(yes)* | Cumulative TCS dose *(increase)* | TCS potency *(greater potency)* | Recency of TCS use *(more recent)* | Duration of TCS use *(longer duration)* |
|---|---|---|---|---|---|---|---|
| Chronic AEs | Musculoskeletal and connective tissue disorders | Osteoporosis | ⚠ 10,19 | ⚠ 10,19 | | | |
| | | Osteoporotic fracture | ⚠ 10,19 | ⚠ 10,19 | | | |
| | Metabolism and nutrition disorders | T2D | ⚠ 11,21 | ⚠ 21 | ⚠ 11 | ⚠ 21 | ⚠ 11,21 |
| | Endocrine disorders[a] | HPA axis suppression | ⚠ 20 | | ⚠ 20 | | |
| | | Cushing syndrome | ⚠ 20 | | ⚠ 20 | | |
| | Adverse fetal outcomes | Low birth weight | ⚠ 22,23 | ⚠ 22 | ⚠ 22 | | |
| | | Small for gestational age | ⚠ 22,23 | ⚠ 22 | ⚠ 22 | | |
| | | Fetal death | ⚠ 23 | | | | |
| | | Orofacial cleft | ⚠ 23 | | | | |
| | | Preterm delivery | ⚠ 23 | | | | |

[a]Erdem et al[20] was a single-center observational study.

**HPA Axis Suppression With TCS Use and Examples of Dosing Thresholds Suggested by Clinical Experience**

**Dose of ointment (BID for 30 days) needed to cover body areas[24]**
- Face and neck: 75 g
- Front of the trunk: 210 g
- Back of the trunk: 210 g
- One arm: 90 g
- One hand (front and back): 30 g

**Some doses may exceed thresholds for HPA axis suppression**

**Examples of dosing thresholds as suggested by Coondoo A, et al.[16]**
- Clobetasol proprionate ointment ~14 g/week may induce HPA suppression in children
- Betamethasone diproprionate 49 g/week reduces plasma cortisol levels
- Very high-potency topical CS (49 g for 2 weeks) causes temporary/reversible HPA suppression

**Safety Risks With Short-Term (<30 Days) Oral CS Use Reported in Population-Based Studies**

| | | | CS use (yes) | Cumulative CS dose *(increase)* | Daily CS dose *(increase)* | Recency of CS use *(more recent)* | Duration of CS use *(longer duration)* |
|---|---|---|---|---|---|---|---|
| Acute AEs | Infections and infestations | Sepsis | ⚠ 3,26 | | ⚠ 3 | ⚠ 3,26 | |
| | GI disorders | Ulcer/GI bleed | ⚠ 26 | | | ⚠ 26 | |
| Chronic AEs | Musculoskeletal and connective tissue disorders | Fracture | ⚠ 3 | | ⚠ 3 | ⚠ 3 | |
| | Cardio/ cerebrovascular disorders | Heart failure | ⚠ 26 | | | ⚠ 26 | |
| | | Venous thromboembolism | ⚠ 3 | | ⚠ 3 | ⚠ 3 | |

**Safety Risks With Long-Term (≥30 days) Oral CS Use Reported in Population-Based Studies (unless otherwise noted)**

| | | CS use (yes) | Cumulative CS dose *(increase)* | Daily CS dose *(increase)* | Recency of CS use *(more recent)* | Duration of CS use *(longer duration)* |
|---|---|---|---|---|---|---|
| Acute AEs | Infections and infestations | ⚠ 30,32,33,36,48,50 | ⚠ 36,48,50 | ⚠ 28,30,32,33,36 | | |
| | GI disorders (ie, ulcer/GI bleed) | ⚠ 30,48 | ⚠ 48 | ⚠ 28,30 | | |
| Chronic AEs | Musculoskeletal and connective tissue disorders (ie, osteoporosis, fracture) | ⚠ 3,14,29-33,42-45,48-51 | ⚠ 42-45,49,50 | ⚠ 3,14,27-34,42-45 | ⚠ 3,42,45,49 | ⚠ 49,51 |
| | Cardio/cerebrovascular disorders (ie, hypertension, MI, stroke) | ⚠ 30-32,35,40,47,48,50 | ⚠ 35,40,47,48,50 | ⚠ 28,30-32,35,40 | ⚠ 40 | ⚠ 35 |
| | Metabolism and nutrition disorders (ie, obesity, T2D) | ⚠ 30-32,39,41,48,50 | ⚠ 39,41,48,50 | ⚠ 28,30-32,39,41 | ⚠ 39,41 | |
| | Eye disorders (ie, cataract) | ⚠ 30,32,50 | ⚠ 50 | ⚠ 28,30,32 | | |
| | Death (ie, all-cause, CV-related death)[a] | ⚠ 37,38 | ⚠ 37,38 | ⚠ 37,38 | ⚠ 37 | |
| | Endocrine disorders (ie, Cushing syndrome) | ⚠ 33 | | ⚠ 33 | | |
| | Kidney disorders (ie, renal impairment) | ⚠ 50 | ⚠ 50 | | | |
| | Neuropsychiatric disorders (ie, depression, anxiety, sleep disorder) | ⚠ 30,33,50 | ⚠ 50 | ⚠ 28,30,33 | | |
| | Respiratory disorders (ie, sleep apnea) | ⚠ 50 | ⚠ 50 | | | |

[a]del Rincón et al[38] was a 6-center prospective study.

## CONCLUSIONS

- **Topical CS:** Available data underscore the importance of routine safety monitoring, application of the lowest dose for the shortest time, and consideration of alternate therapies[58] when high doses, extensive body surface areas, or prolonged exposure to topical CS are required for self-limiting dermatoses
  - Of note, case studies have reported an association between TCS use and ocular AEs (ie, glaucoma, cataract)[58-61]; however, no population-based studies regarding a potential association were identified in this targeted literature review
- **Oral CS:** Findings from recent large-scale studies show that AEs are associated even with low doses (5–10 mg prednisone equivalent/day) or short-term oral CS use, including clinically meaningful risks of HPA axis suppression, T2D, osteoporosis, osteoporotic fractures, and other systemic AEs
- These results underscore the importance of a more discriminating approach to CS use, especially given the increasing availability of novel, effective alternatives and identifies an opportunity for a new era where non-CS therapies are used as replacements for topical CS to minimize patient risk without compromising treatment outcomes

## ABBREVIATIONS

AE, adverse effect; BID, twice daily; CS, corticosteroid; CV, cardiovascular; CVD, CV disease; GI, gastrointestinal; HPA, hypothalamic-pituitary-adrenal; PsO, psoriasis; T2D, type 2 diabetes; TCS, topical corticosteroid; US, United States.

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