Rational Use of Topical Glucocorticoids

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Introduction

Topical corticosteroids have a major role in the management of many skin diseases. They exert anti-inflammatory, antimitotic, and immunosuppressive effects through a variety of mechanisms.

Vehicles and Formulations

Θ Available in a variety of *vehicles* and formulations

Θ Role of vehicles

- Rapid *delivery* of the drug to the stratum corneum and into the lower layers of the skin
- Easy to apply and *cosmetically* acceptable
- Provide a medium in which the drug remains *stable*

Topical therapy: Formulation selection for specific body sites

Formulation	Smooth, nonhairy skin; thick, hyperkeratotic lesions	Hairy areas	Palms, soles	Infected areas	Between skin folds; moist, macerated lesions
Ointment	+++		+++		
Cream	++	+	++	+	++
Lotion		++		++	++
Solution		+++		+++	++
Gel		++		+	+
Foam	++	+++	++	++	++

+: infrequently used; ++: acceptable vehicle; +++: preferred vehicle.

Adapted from: Goldstein BG, Goldstein AO. Practical Dermatology 2nd ed, Mosby-Year Book, Inc, St. Louis, MO, 1997.

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Vehicles and Formulations

If the *wrong formulation* is used, the **response** to therapy may be delayed, inadequate, or, in some cases, **worsened**. As an example, the use of a corticosteroid *gel* on fissured hand eczema will cause increased pain and stinging due to the *alcohol* base of the gel. Treating a moist lesion with an ointment may cause folliculitis secondary to its occlusive properties.

Vehicles and Formulations

- **Ointments**
  - Consist predominantly of water suspended in oil
  - An excellent lubricant
  - Semi-occlusive
  - Are generally the **most potent** formulations due to their occlusive effect
  - Patient acceptance and *adherence* to treatment may be **low** because they are greasy, sticky, and generally unsuitable for application to large body areas or to hairy areas
  - Decreases transepidermal water loss
  - Provides enhanced medication absorption

Vehicles and Formulations

- **Lotions**
  - Suspensions or solutions of medication in water, alcohol, or other liquids (*shake* well before use)
  - Are especially useful in *hairy areas* and in conditions where *large areas* have to be treated
  - They provide a *cooling* and drying effect, making them useful for treating moist dermatoses and/or pruritus
- **Creams**
  - Semisolid emulsions of 20 to 50 percent oil in water
  - *Cosmetically* appealing and can be washed off with water
  - Usually stronger than lotions but less potent than ointments

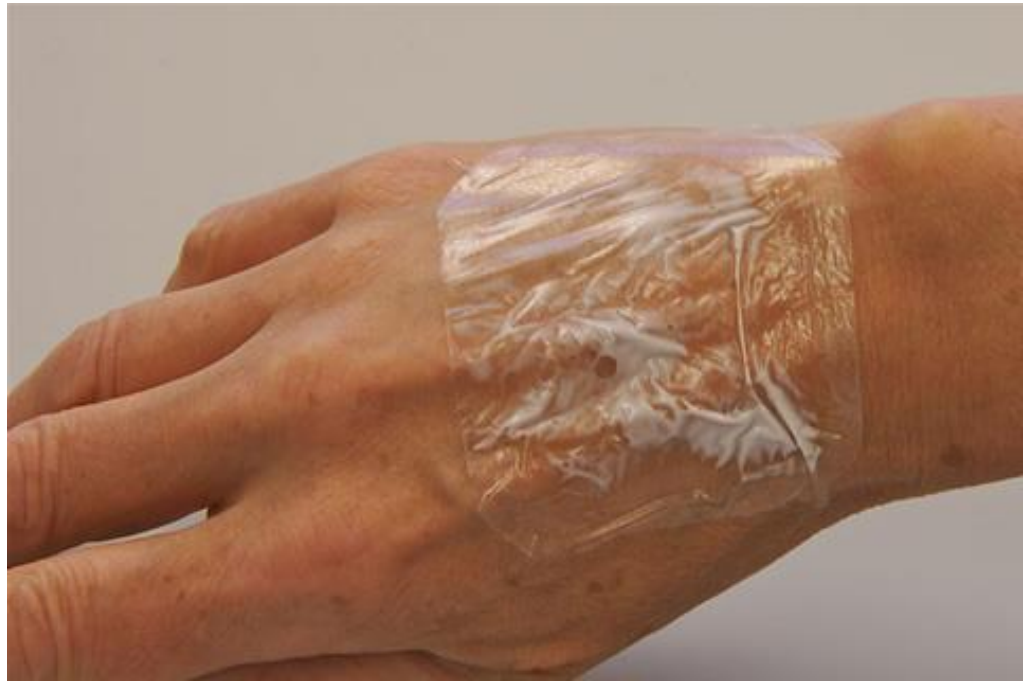
Vehicles and Formulations

- **Gels**
  - Oil-in-water emulsion with alcohol in the base
  - Dry in a *thin*, greaseless, *non-staining* film
  - Combine the best therapeutic *advantages* of **ointments** with the best *cosmetic* advantages of **creams**
  - *Cosmetically attractive* to many patients
  - Gels are transparent, colorless, semisolid emulsions that *liquefy* on contact with the skin.
  - *Easily absorbed* and are an efficient method for delivering topical corticosteroids to **hair-bearing areas**

Potency

According to the United States classification system, *topical corticosteroids* can be subdivided into **seven groups**, with group 1 being the most potent and group 7 the least potent.

Occlusive dressings promote cutaneous hydration and significantly increase absorption and potency. Occlusion can enhance topical corticosteroid potency by as much as 100-fold

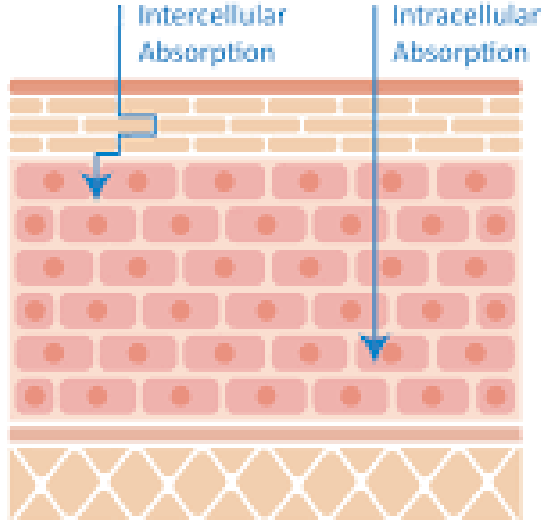


Potency group*	Corticosteroid	Vehicle type/form	Available strength(s), percent
Super-high potency (group 1)	Clobetasol propionate	Cream Lotion Ointment	0.05 0.05 0.05
High potency (group 2)	*Betamethasone dipropionate* *Clobetasol propionate*	*Ointment* *Cream*	*0.05* *0.025*
High potency (group 3)	Betamethasone valerate Mometasone furoate	Ointment Ointment	0.1 0.1
Medium potency (group 4)	Fluocinolone acetonide Mometasone furoate Triamcinolone acetonide	Ointment Cream, lotion, solution Cream Ointment	0.025 0.1 0.1 0.1
Lower-mid potency (group 5)	Betamethasone valerate Fluocinolone acetonide Desonide	Cream Cream Ointment Gel	0.1 0.025 0.05 0.05
Low potency (group 6)	Betamethasone valerate Desonide	Lotion Cream *Lotion*	0.1 0.05 *0.05*
Least potent (group 7)	Hydrocortisone (base, <2%) Hydrocortisone acetate	Ointment Cream	1 1

Percutaneous Absorption

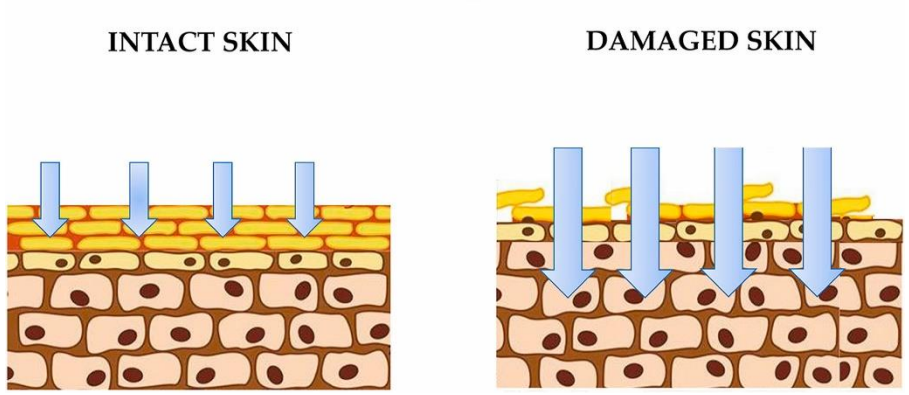
The percutaneous absorption of topical corticosteroids depends on several factors:

- Type of corticosteroid and bioavailability
- Vehicle
- Integrity of the skin barrier
- Use of occlusive dressings
- Surface area
- Anatomic region
- Frequency and duration of treatment
- Presence of inflammation



Percutaneous Absorption

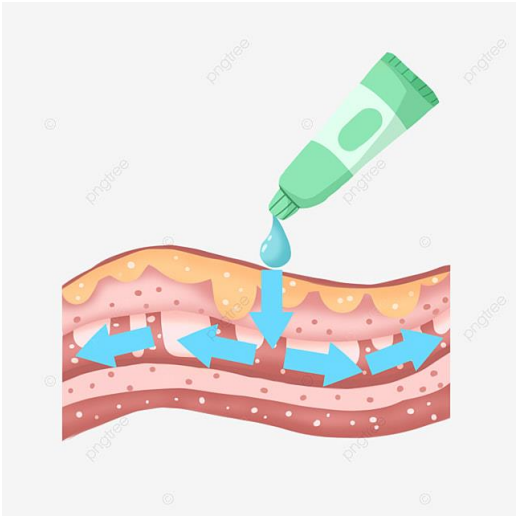
Systemic absorption is **higher** in areas of *inflamed skin*, compared with intact skin, as well as through the thin stratum corneum of *infants*' skin, compared with adult skin. Furthermore, anatomic regions with a *thin epidermis* are significantly more permeable to topical steroids than *thick-skinned* areas.



Percutaneous Absorption

Regional differences in percutaneous absorption (percent of the total dose absorbed across the body) are as follows:

Sole – 0.05 percent
Palm – 0.1 percent
Forearm – 1 percent
Scalp – 3.5 percent
Face – 7 percent
Eyelids and genitalia – 30 percent



Corticosteroid Selection and Administration

General principles

The corticosteroid selection depends, to some extent, upon the *condition being treated*. In general, it is best to *start* with the **lowest potency** agents needed and use for **as short a period** of time as possible.

Table 2. Common skin conditions treatable with topical corticosteroid (TCS) agents[15-17]

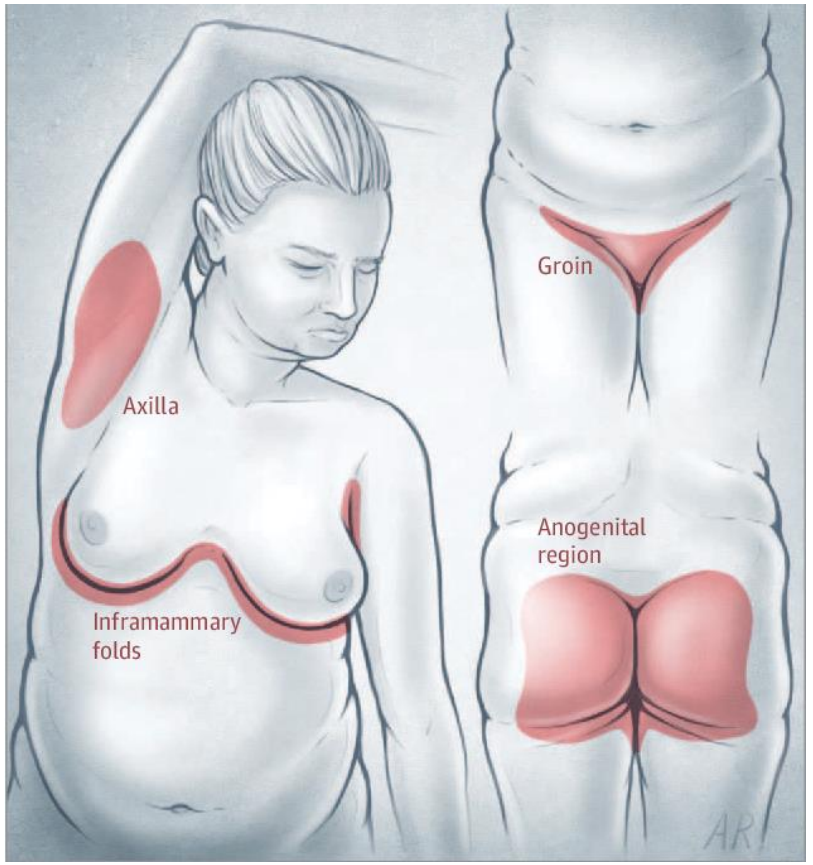
Mild (low) potency TCS	• Dermatitis (face, eyelids, napkin area) • Intertrigo • Perianal inflammation
Mild-to-moderate potency TCS	• Atopic dermatitis • Asteatotic eczema • Contact dermatitis • Dry nummular eczema • Perianal inflammation (severe) • Intertrigo (short term) • Scabies (after scabicide) • Seborrhoeic dermatitis
Moderate-to-potent/ ultrapotent TCS	• Atopic dermatitis (severe) • Alopecia areata • Contact dermatitis (severe) • Eczema of hyperkeratotic, exudative nummular, hand and feet • Granulomatous skin disorders – Granuloma annulare, Necrobiosis lipoidica, and sarcoidosis • Lupus erythematosus • Lichen – simplex chronicus, planus and sclerosus • Pemphigus and pemphigoid • Psoriasis • Stasis dermatitis • Vitiligo

Corticosteroid Selection and Administration

General recommendations

- **Super high-potency** corticosteroids are generally used for *severe dermatoses* over *nonfacial/nonintertriginous* areas (eg, psoriasis, severe atopic dermatitis, severe contact dermatitis). They are especially useful over the *palms* and *soles*, which tend to resist topical corticosteroid penetration due to the thick stratum corneum.

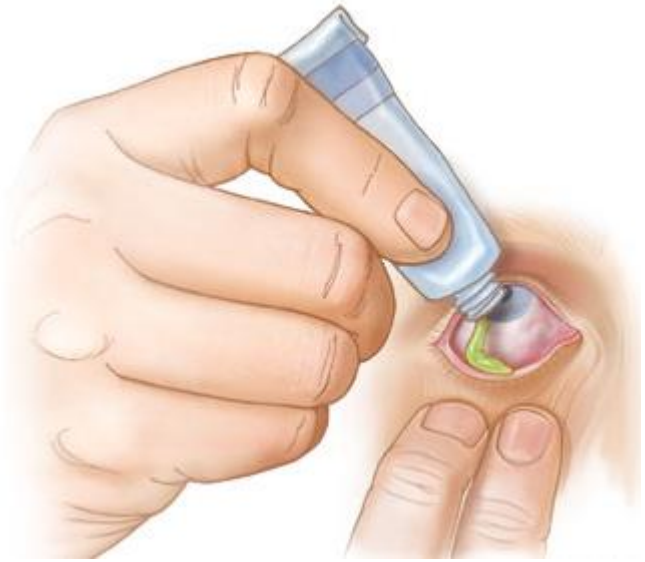
- **Medium- to high-potency** strength preparations are appropriate for *mild to moderate nonfacial/nonintertriginous* dermatoses.



Corticosteroid Selection and Administration

- *Eyelid* and *genital* dermatoses should be managed with **low-potency** topical corticosteroids for limited time periods.

- *Low* to *medium* strength preparations should be considered when **large areas** are treated because of the likelihood of systemic absorption.



Corticosteroid Selection and Administration

Mode of application

For optimal absorption, it is advised to apply topical corticosteroids to **moist skin** either immediately after bathing or after wet soaks ("soak and smear"). Creams and ointments should be **rubbed** in *until they disappear*, since there is no advantage in leaving a thick layer on the skin. **Occlusive dressings** will enhance drug absorption, often by a factor of 10.

Corticosteroid Selection and Administration

In terms of *frequency*, a **once-daily** regimen is generally recommended for better *compliance*. Twice-daily application may be considered for the *initial week(s)* for certain severe lesions, reducing to daily or alternate-day application depending on the response.

Corticosteroid Selection and Administration

Amount and frequency of application

Topical corticosteroids are usually applied *once* or *twice* daily. However, twice-daily application may **not** be more effective than once daily, while *increasing* the *systemic exposure* to the drug and costs.

"The fingertip unit (FTU)"

Corticosteroid Selection and Administration

On average, the number of FTUs needed in certain body areas are as follows:

Face and neck – 2.5

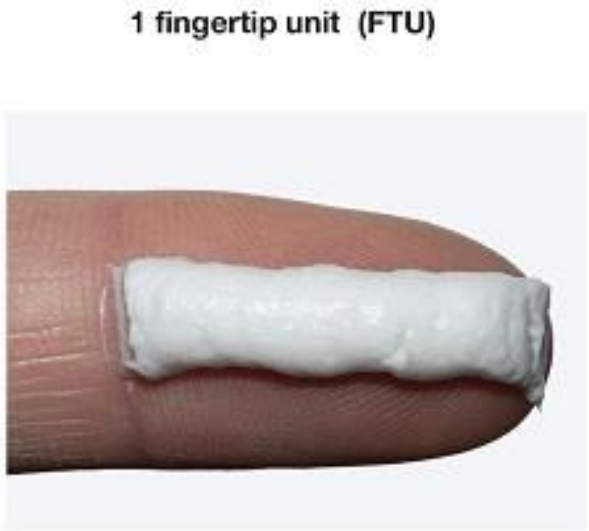
Trunk (front or back) – 7

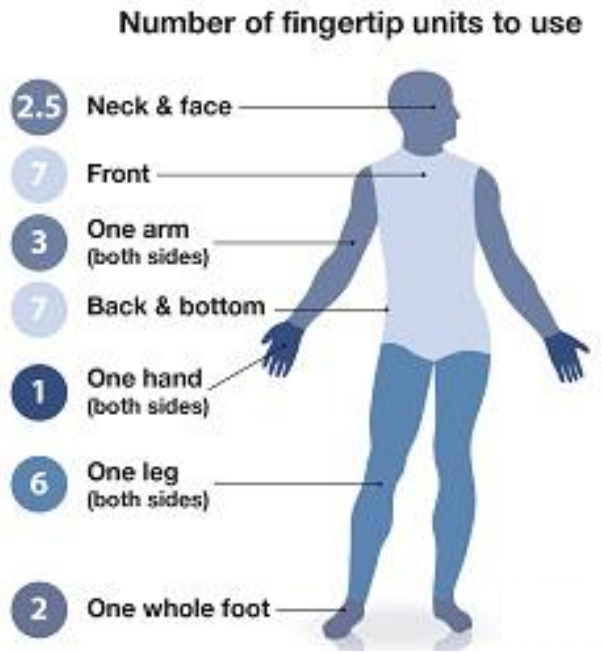
One arm – 3

One hand (dorsum or palm) – 0.5

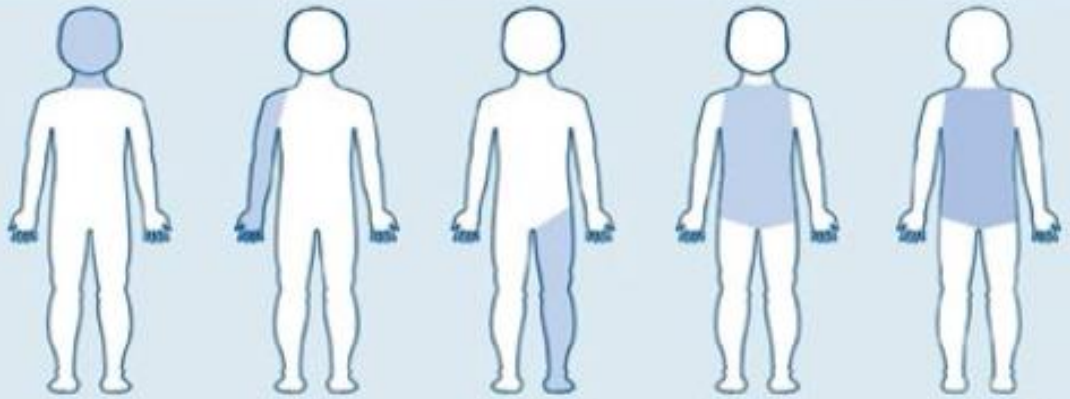
One leg – 6

One foot – 2





Corticosteroid Selection and Administration



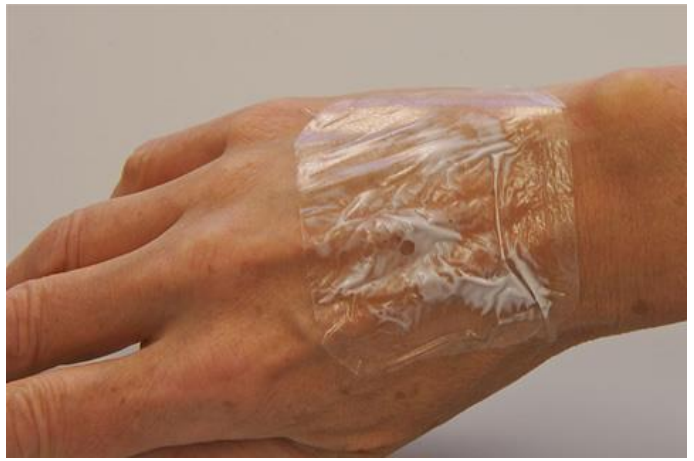
AGE	NUMBER OF FTU				
3–6 months	1	1	1.5	1	1.5
1–2 years	1.5	1.5	2	2	3
3–5 years	1.5	2	2	3	3.5
6–10 years	2	2.5	4.5	3.5	5

Corticosteroid Selection and Administration

It is highly recommended to use *adjunct moisturizers/emollients* following application of topical corticosteroids to affected areas. The moisturizer can be applied locally or to the whole body to **ease pruritus** and **irritation** by maintaining optimum skin moisture. The moisture alone is also useful as a *steroid-sparing* agent in trivial dermatitis.

Corticosteroid Selection and Administration

An **occlusive dressing** with appropriate cover, such as a tubular bandage or plastic wrap, is favorable for severe and thick/keratotic/lichenified lesions. Occlusion with a non-irritant *glove* or *sock* can also be used for lesions of the *hand* or *foot*, respectively.



Corticosteroid Selection and Administration

Treatment duration and tapering

The duration of *daily use* of **super high-potency** topical corticosteroids should not exceed four weeks if possible, although persistent lesions on small areas may be safely treated for a longer time.

High-potency and **medium-strength** preparations rarely cause cutaneous side effects if used for less than six to eight weeks, although they can occur with shorter courses of treatment, especially on the face and intertriginous areas.

Corticosteroid Selection and Administration

Facial, *intertriginous*, and *genital* dermatoses should be treated for short courses of one to two weeks, preferably with **low- to mid-potency** topical corticosteroids, since these areas are most susceptible to corticosteroid-induced atrophy, telangiectasia, and acneiform eruption.

Corticosteroid Selection and Administration

Topical corticosteroids should be *discontinued* when the skin condition has *resolved*. **Rebound flares** can be avoided by *tapering* topical therapy with a gradual reduction of both potency and dosing frequency at *two-week intervals*.

Use in Children

The use of *lower-potency* (groups **4 to 7**) topical corticosteroids in children is generally *safe* when used for short durations and for appropriate inflammatory conditions.

Children under *age 12 years* typically **should not** use *potent* or *superpotent* topical corticosteroids. An *exception* can be made for very severe inflammatory dermatoses (e.g., psoriasis, severe atopic dermatitis), for which short courses (up to two weeks) of more potent (groups 1 to 3) topical corticosteroids may be warranted.

Use in Children

To *minimize* the risk of side effects:

- Avoid use of **high-potency** corticosteroids on the *face*, *intertriginous* areas, or other *thin-skinned*, highly penetrable areas (e.g., the perineum, axillae).
- High-potency corticosteroids should ideally be used only *once a day*.
- High-potency corticosteroids should not be administered for longer than *two weeks*.

Use During Pregnancy or Lactation

Based on the available evidence, the use *low- to mid-potency* topical corticosteroids does **not** seem to increase the risk of adverse outcomes for the mother and the fetus, including preterm delivery, birth defects, and low birth weight.

Because an association between *prolonged* maternal use of *potent* topical corticosteroids and **low birth weight** cannot be excluded with certainty, it is prudent that pregnant women use *low- or mid-potency* topical corticosteroids rather than potent or superpotent preparations.

Use During Pregnancy or Lactation

If potent or superpotent topical corticosteroids are needed, they should be used for a *short time*, the *amount* used should be kept to a *minimum*, and *fetal growth* should be monitored.

Use During Pregnancy or Lactation

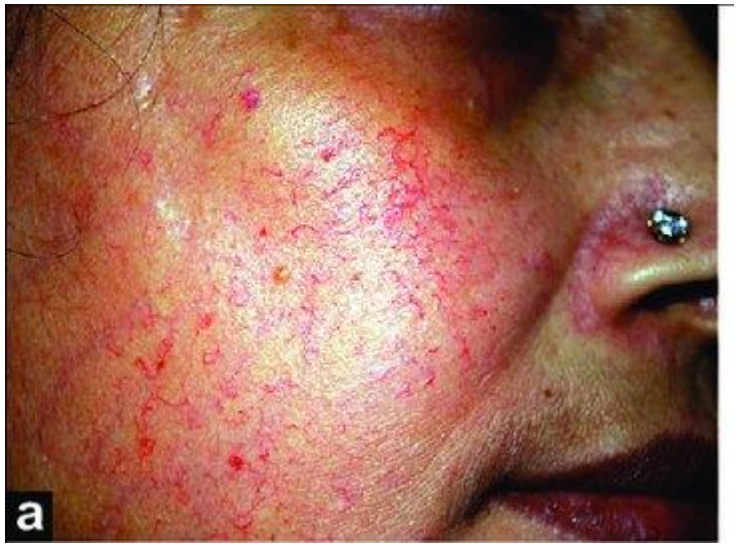
It is **not known** whether topical corticosteroids are secreted in *breast milk*; **no adverse effects** have been noted in lactating women. The drugs should not be applied to the *nipples* prior to nursing.

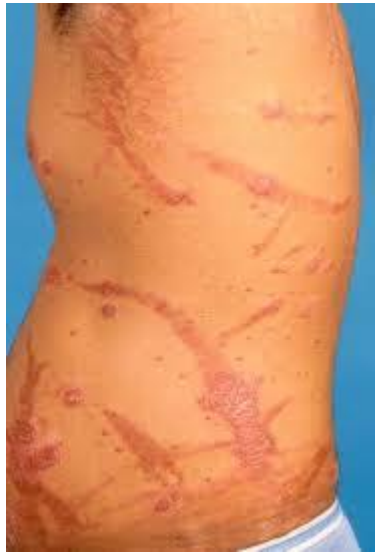
Adverse Effects

Cutaneous

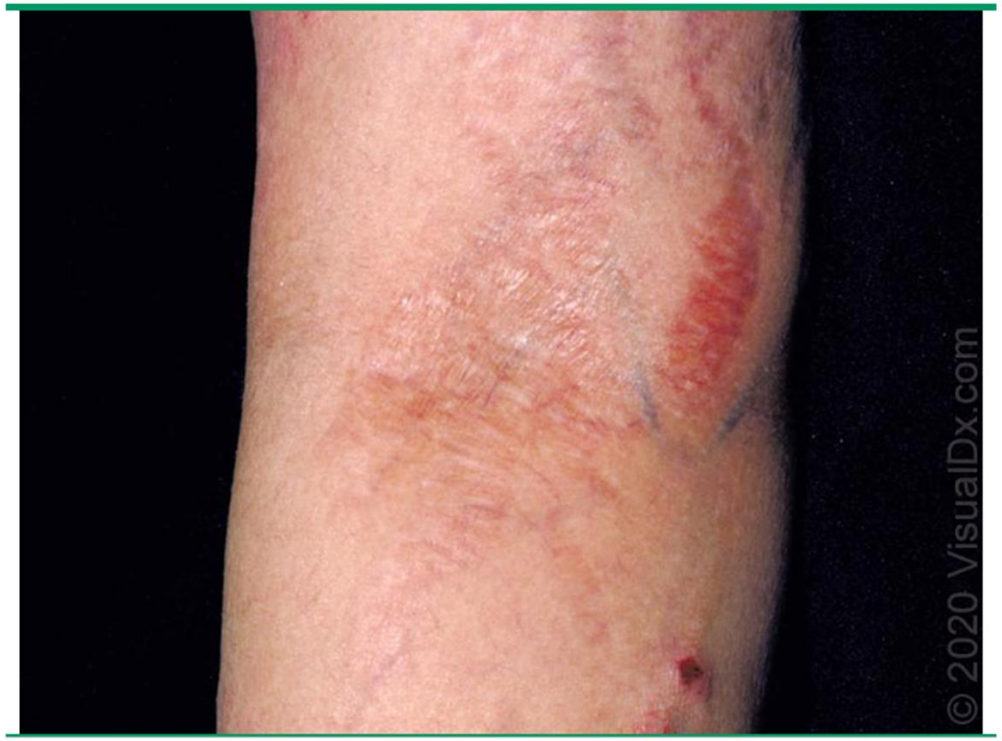
- **Atrophy, telangiectasia, striae**
  - As early as *two to three weeks* following daily application of **potent** or **superpotent** corticosteroids.
  - *Intertriginous* and *thin-skinned*, highly penetrable areas (eg, eyelid, face in general, genitals) are particularly susceptible to atrophy, which usually recovers within weeks to months if therapy is discontinued as soon as atrophic change occurs.

Adverse Effects





Cutaneous atrophy caused by topical corticosteroids



A shiny, atrophic plaque in the antecubital fossa and surrounding white and bright red, curvilinear plaques (striae).

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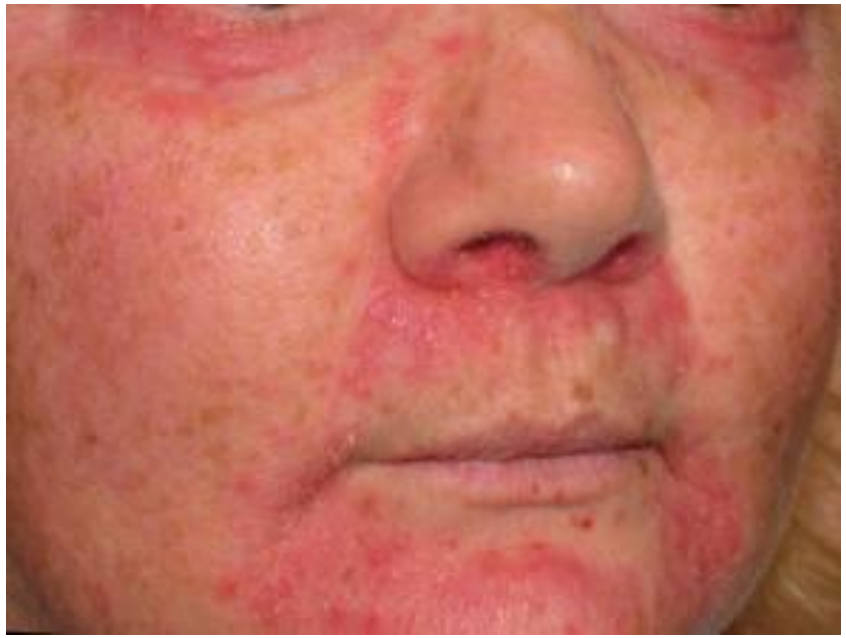
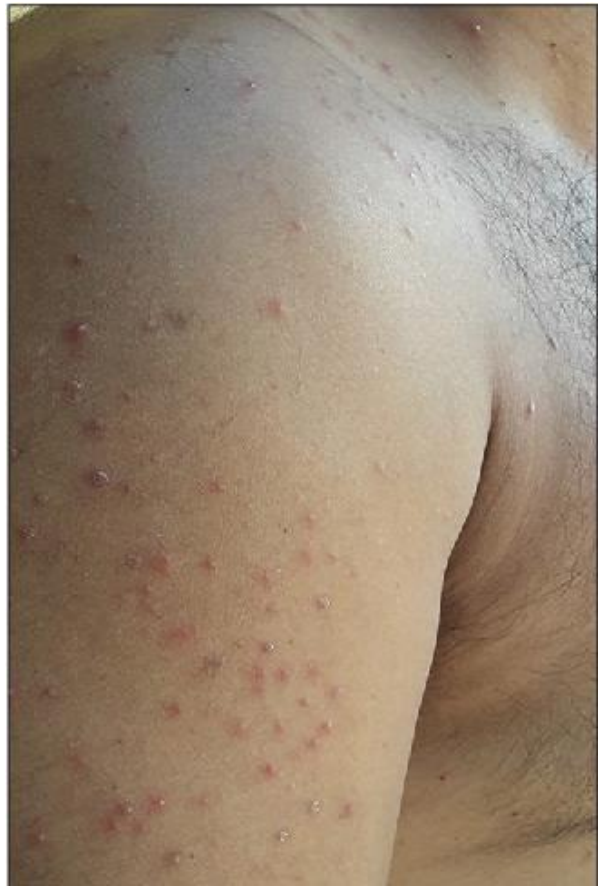
Adverse Effects

- **Acneiform eruption**
  - Occurs after prolonged use
  - Perioral dermatitis





Adverse Effects

- **Withdrawal syndrome**
  - Occurs after *prolonged use*, especially on the face or genitals
  - Signs and symptoms including erythema, burning or stinging sensation, pruritus, pain, and facial hot flashes

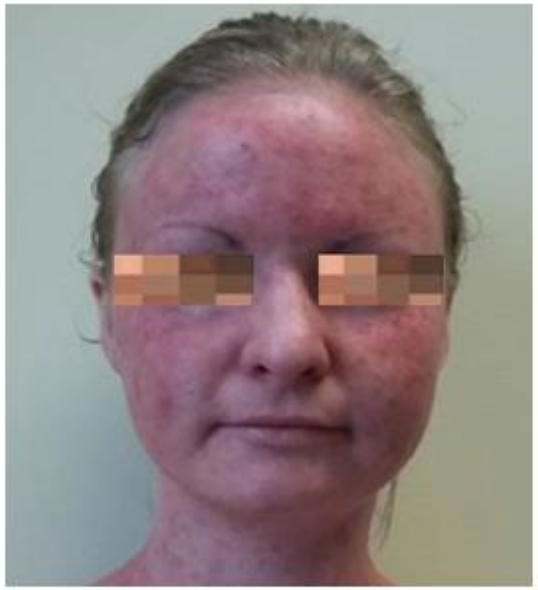


Fig 3. Papulopustular subtype of steroid withdrawal syndrome. Erythema, papules, and pustules.

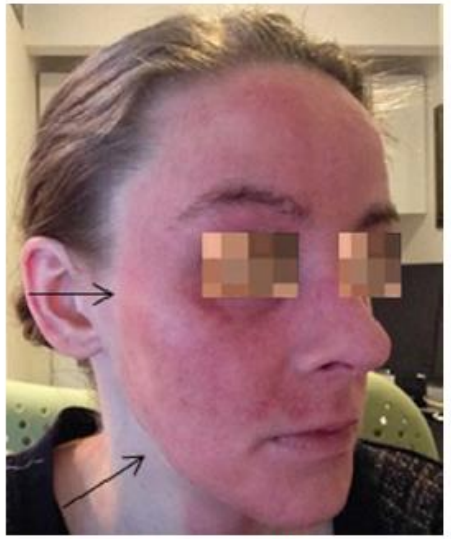


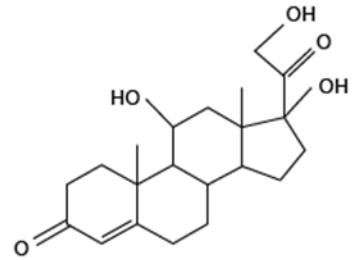
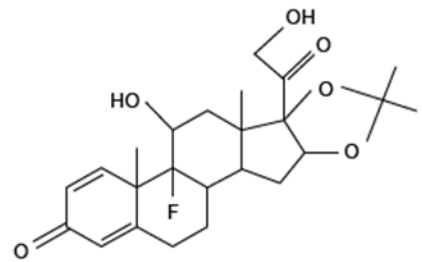
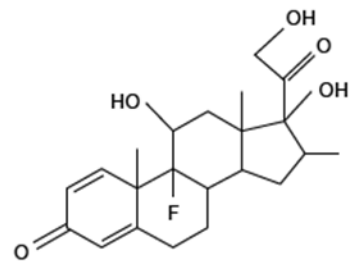
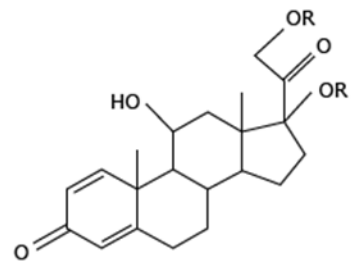
Fig 2. Erythematoedematous subtype of steroid withdrawal syndrome. Edema and erythema with a sharp cutoff (*arrows*) line between red and normal-looking skin. The patient reported a burning sensation.

Adverse Effects

- **Allergic sensitization**
  - *Vehicles* or *preservatives* are most often the sensitizing agents
  - Contact allergy against the *steroid moiety* itself is possible
  - Allergy should be suspected in patients with chronic dermatoses that appear to be *exacerbated* by therapy
  - Patch testing is useful
  - Cross-reactions between different topical corticosteroids

  - Cross-reactivity between groups is not uncommon
  - Class C topical corticosteroids have the *lowest rate* of allergenicity

Coopman classification of cross-reactivity in allergic reactions to topical corticosteroids

Class	Example	Glucocorticoid	Structure
A	Hydrocortisone type without substitution on the D-ring or C17 carbon chain, but including C17 and/or C21 acetate esters	▪ Hydrocortisone (acetate, succinate, phosphate) ▪ Methylprednisolone acetate (acetate, succinate, phosphate) ▪ Prednisolone ▪ Prednisolone acetate ▪ Tixocortol pivalate	
B	Triamcinolone acetonide type C16, C17-*cis*, diol or ketal chain	▪ Amcinonide ▪ Budesonide ▪ Desonide ▪ Flunisolide ▪ Fluocinolone acetonide ▪ Fluocinomide ▪ Halcinonide ▪ Triamcinolone ▪ Triamcinolone acetonide	
C	Betamethasone type C16 alkyl substitution	▪ Betamethasone ▪ Desoximetasone ▪ Dexamethasone ▪ Paramethasone ▪ Flucortolone	
D	Hydrocortisone-17-butyrate type C17 and/or C21 long-chain ester	▪ Beclomethasone dipropionate (D1) ▪ Betamethasone valerate (D1) ▪ Betamethasone dipropionate (D1) ▪ Clobethasone-17-butyrate (D1) ▪ Clobetasol-17-propionate (D1) ▪ Fluticasone and prednicarbate (D2) ▪ Mometasone (D1) ▪ Hydrocortisone-17-butyrate (D2) ▪ Hydrocortisone-17-propionate (D2) ▪ Methylprednisolone aceponate (D2)	

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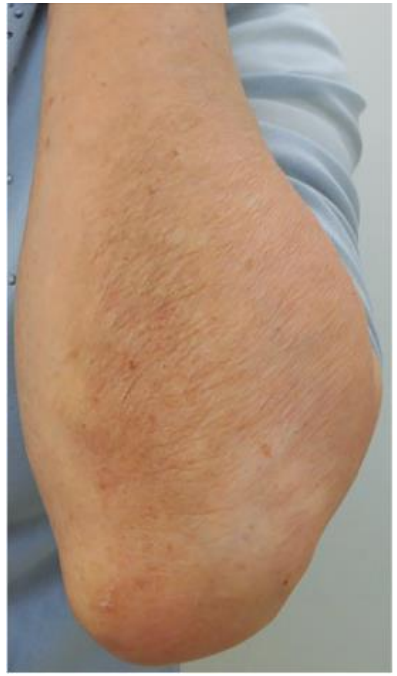
Adverse Effects

- **Other:**
  - Purpura
  - Changes in pigmentation
  - Hypertrichosis



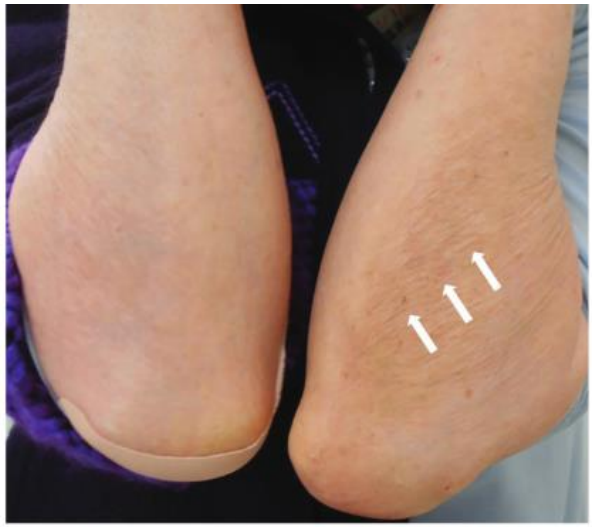
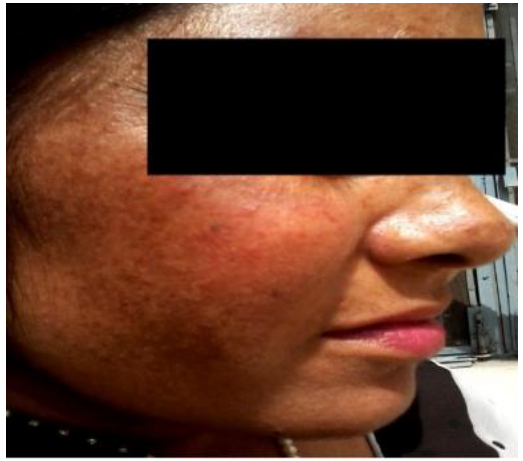
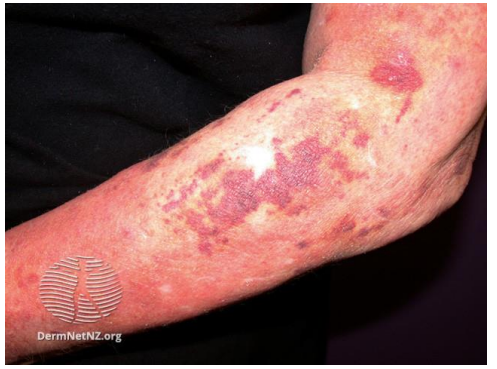


Figure 2. Arrows point to striae atrophicae on the patient's left forearm. Hair growth on the right forearm is normal.





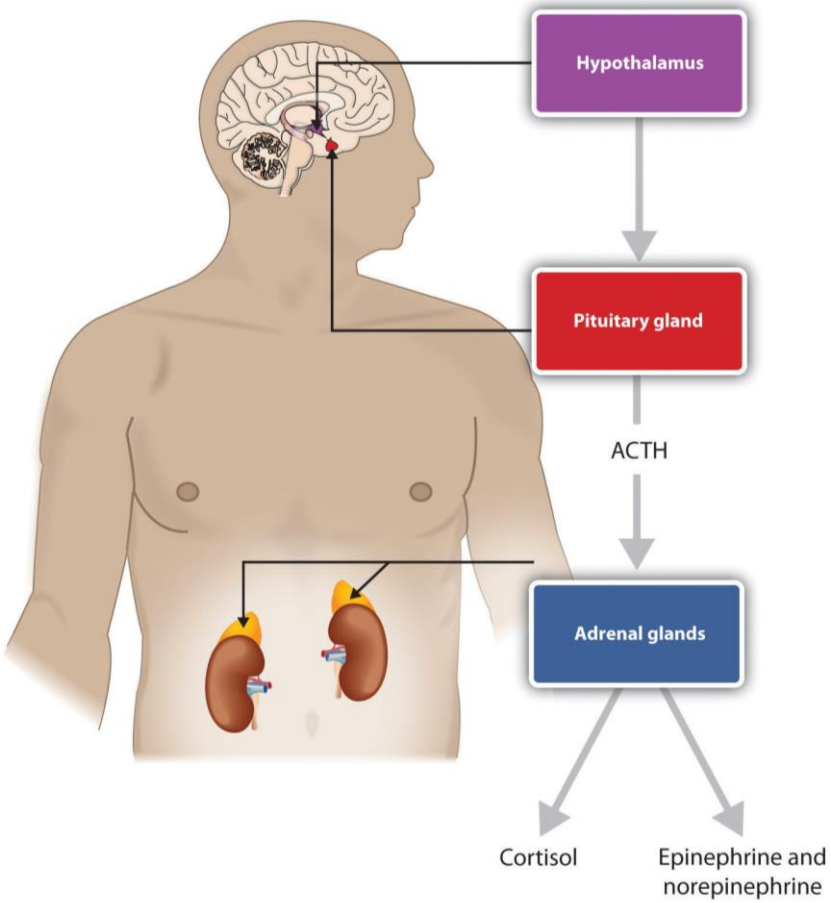
Adverse Effects

Systemic

- **Hypothalamic-pituitary axis (HPA) suppression**
  - With super high-potency and high-potency topical corticosteroids
  - Risk factors: use of high-potency corticosteroids, chronic use, application to highly permeable areas, treatment of large areas, occlusion, altered skin barrier, and young age.

- **Hyperglycemia** and unmasking of latent diabetes mellitus

- **Bone mineral density**: No effect



Adverse Effects

Study or Subgroup	log[Odds Ratio]	SE	Cases Total	Controls Total	Weight	Odds Ratio IV, Random, 95% CI
Anderson (Denmark) 2019	0.3001	0.0094	115218	115218	33.4%	1.35 [1.33, 1.38]
Anderson (UK) 2019	0.207	0.0166	54944	54944	32.1%	1.23 [1.19, 1.27]
Gulliford 2006	0.0953	0.0741	688	1085	15.6%	1.10 [0.95, 1.27]
van der Linden 2009	0.1823	0.0612	2212	8582	18.9%	1.20 [1.06, 1.35]
Total (95% CI)			**173062**	**179829**	**100.0%**	**1.24 [1.15, 1.34]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 32.06$, df = 3 ($P < 0.00001$); $I^2 = 91\%$

Test for overall effect: $Z = 5.42$ ($P < 0.00001$)

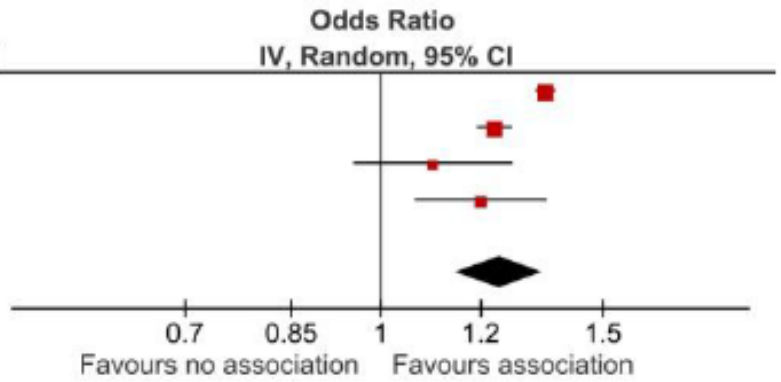


Figure 1. Forest plot demonstrating significant association between topical corticosteroid use and development of new Type 2 diabetes mellitus.

Adverse Effects

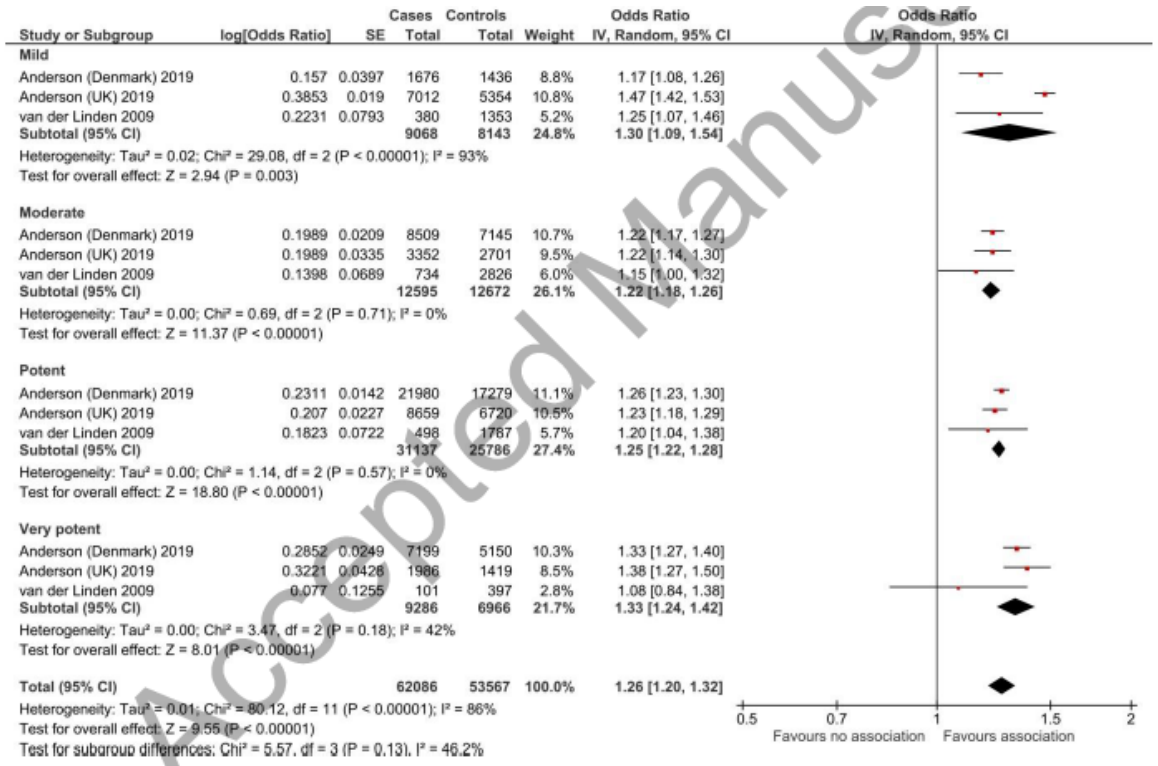


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Figure 2. Forest plot demonstrating risk of developing Type 2 diabetes mellitus with mild, moderate, potent and very potent classes of topical corticosteroids.

Adverse Effects

Tachyphylaxis

- **Not confirmed** in clinical settings

- The patients' *lack of adherence* to treatment over time may account for apparent reductions in topical corticosteroid efficacy