ClinicalEvidence

# Wrinkles

**February 2014**

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## ABSTRACT

INTRODUCTION: Skin disorders associated with photodamage from ultraviolet light include wrinkles, hyperpigmentation, tactile roughness, and telangiectasia, and are more common in people with white skin compared with other skin types. Wrinkles are also associated with ageing, hormonal status, smoking, and intercurrent disease. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for skin wrinkles? We searched: Medline, Embase, The Cochrane Library, and other important databases up to February 2014 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 33 studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: botulinum toxin injection (e.g., botulinum toxin type A and type B), carbon dioxide laser, chemical peel (including alpha and beta hydroxyl acids), dermabrasion, isotretinoin, tazarotene, tretinoin, and variable pulse erbium:YAG laser.


## QUESTIONS



## INTERVENTIONS



## Key points

- Skin disorders associated with damage by ultraviolet light include wrinkles, hyperpigmentation, tactile roughness, and telangiectasia, and are more common in people with white skin compared with those with other skin types.

  Wrinkles are also associated with ageing, hormonal status, smoking, and intercurrent disease.

- Exposure to ultraviolet light may be associated with photodamage to the skin. Guidelines suggest that avoiding direct sunlight, either by staying indoors or in the shade, or by wearing protective clothing, is the most effective measure for reducing exposure to ultraviolet light.

- Botulinum toxin injection (given in a single session) seems to be more effective than placebo at improving wrinkles at up to 120 days.

  We found no RCTs comparing repeated injections of botulinum toxin versus placebo over a long period of time.

- Topical tretinoin may improve fine wrinkles when applied daily, compared with vehicle cream, in people with mild to severe photodamage, but its effect on coarse wrinkles is unclear.

  Topical tretinoin may cause itching, burning, erythema, and skin peeling.

  Isotretinoin cream applied daily may improve fine and coarse wrinkles compared with vehicle cream in people with mild to severe photodamage, but may cause severe irritation of the face.

- Tazarotene applied daily may improve the appearance of fine wrinkles compared with placebo/vehicle cream. However, it can cause burning of the skin.

  We don't know whether tazarotene is more effective than tretinoin at improving fine and coarse wrinkles in people with moderate photodamage, as studies have given inconclusive results.

- We don't know whether chemical peel (including alpha and beta hydroxyl acids) is beneficial.

- We don't know whether dermabrasion is more effective at improving wrinkles compared with carbon dioxide laser treatment, as studies have given inconclusive results, but adverse effects are common with both treatments, especially erythema.

  We don't know whether variable pulse erbium:YAG laser treatment improves wrinkles, as few studies were found.

## Clinical context

**DEFINITION**

Wrinkles are visible creases or folds in the skin. Wrinkles less than 1 mm in width and depth are defined as fine wrinkles. Wrinkles that are 1 mm or more in width and depth are defined as coarse wrinkles. Most RCTs have studied wrinkles on the face, forearms, and hands.

**INCIDENCE/ PREVALENCE**

We found no information on the incidence of wrinkles alone, only on the incidence of skin photodamage, which includes a spectrum of features such as wrinkles, hyperpigmentation, tactile roughness, and telangiectasia. The incidence of skin disorders associated with ultraviolet light increases with age and develops over several decades. One Australian study (1539 people, aged 20–55 years, living in Queensland) found moderate to severe photodamage in 72% of men and 47% of women under 30 years of age. [1] Severity of photodamage was significantly greater with increasing age, and was independently associated with solar keratoses and skin cancer. Wrinkling was more common in people with white skin (especially skin phototypes I and II). We found few reports of photodamage in black skin (phototypes V and VI). One study reported that the incidence of photodamage in European and North American populations with Fitzpatrick skin types I, II, and III is about 80% to 90%. [2] As Asian skin is more pigmented (Fitzpatrick skin types III–V), wrinkling is not readily apparent until approximately the age of 50 years, with wrinkles being less severe than in white skin of similar age. A prospective study (85 white women living in North America and 70 Japanese women living in Tokyo, aged 20–69 years) comparing age-related changes in wrinkles in eight areas of the facial skin (forehead, glabella, upper eyelid, corner of the eye, lower eyelid, nasolabial groove, cheek, and corner of the mouth) and sagging in the subzygomatic area found more wrinkle formation in all areas of the face in younger age groups of white women than in Japanese women (aged 20–29 years). [3] Another prospective study (160 Chinese women and 160 French women, aged 20–60 years) found that wrinkle onset was delayed by about 10 years in Chinese women compared with French women. [4]

**AETIOLOGY/ RISK FACTORS**

Wrinkles may be caused by intrinsic factors (e.g., ageing, hormonal status, and intercurrent diseases) and by extrinsic factors (e.g., exposure to ultraviolet radiation and cigarette smoke). These factors contribute to epidermal thinning, loss of elasticity, skin fragility, and creases and lines in the skin. The severity of photodamage varies with skin type, which includes skin colour and the capacity to tan. [5] It is becoming increasingly clear that brief incidental sun exposures, which occur during the activities of daily living, add significantly to the average individual's daily exposure to ultraviolet light. One review of five observational studies found that facial wrinkles in men and women were more common in smokers than in non-smokers. [6] It also found that the risk of moderate to severe wrinkles in lifelong smokers was more than twice that in current smokers who had been smoking for a shorter period (RR 2.57, 95% CI 1.83 to 3.06). A twin study (67 pairs of Japanese monozygotic twins) found that facial texture or wrinkle scores were significantly higher in twins who smoked or did not use skin protection compared with twins not exposed to cigarettes or using skin protection ($P = 0.04$ and $P = 0.03$, respectively). [7] Another study (400 German women, aged 70–80 years) found a significant correlation between exposure to air pollutants and signs of extrinsic skin ageing, including wrinkles. [8] The effects of pregnancy and menopause on facial wrinkling have also been investigated by some researchers. In postmenopausal women, oestrogen deficiency is thought to be an important contributory factor for development of wrinkles. [9] One observational study (186 Korean women, aged 20–89 years) found that facial wrinkling increased significantly with an increase in the number of full-term pregnancies (OR 1.84, 95% CI 1.02 to 3.31) and the number of years since menopause (OR 3.91, 95% CI 1.07 to 14.28). [10] However, postmenopausal women who had HRT had significantly less facial wrinkling compared with postmenopausal women who had no history of HRT (OR 0.22, 95% CI 0.05 to 0.95). [10] The effects of sleep positioning and facial wrinkles have also been studied. One cross-sectional study (100 US women, aged 23–71 years) found no significant correlation between sleep side preference and the appearance of wrinkles. [11]

**PROGNOSIS**

Wrinkles cannot be considered a medical illness requiring intervention, but concerns about changes in physical appearance brought on by ageing can have a detrimental effect on quality of life. In some cases, concerns about physical appearance can affect personal interactions, occupational functioning, and self-esteem. [12] Geographical differences, culture, and personal values potentially influence a person's anxieties about ageing. In societies in which the maintenance of a youthful appearance is valued, the demand for interventions that ameliorate visible signs of ageing grows as ageing populations expand.

**AIMS OF INTERVENTION**

To improve fine and coarse wrinkling in adults, and to improve quality of life, with minimal adverse effects.

**OUTCOMES**

**Wrinkle improvement** includes physician and participant evaluation of improvement in skin texture that reduces the visibility of wrinkles; **quality of life**; adverse effects. We excluded RCTs based

solely on non-clinical outcomes, such as histological assessment, photography, or optical profilometry.

**METHODS**

*Clinical Evidence* search and appraisal February 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to February 2014, Embase 1980 to February 2014, and The Cochrane Database of Systematic Reviews, issue 1 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language, at least single-blinded, and containing 20 or more people (10 in each arm), of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. Most RCTs in the review recruited people with moderate to severe photodamage and wrinkles, rather than people with wrinkles alone. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 46 ). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

**QUESTION** **What are the effects of treatments for skin wrinkles?**

**OPTION** **TAZAROTENE**

- For GRADE evaluation of interventions for Wrinkles, see table, p 46 .
- Tazarotene applied daily may improve the appearance of fine wrinkles compared with placebo/vehicle cream. However, it can cause burning of the skin.
- We don't know how tazarotene and tretinoin compare at improving fine and coarse wrinkles in people with moderate photodamage, as studies have given inconclusive results.

## Benefits and harms

### Tazarotene versus placebo/vehicle cream:

We found one systematic review (search date 2002, [13] 2 RCTs) and one additional RCT. [14] One RCT identified by the review reported on improvement of other outcomes in the forearm but not improvement in facial wrinkles and, therefore, the data were not analysed.

#### Wrinkle improvement

*Tazarotene compared with placebo/vehicle cream* Daily application of tazarotene may improve the appearance of wrinkles at 24 weeks compared with placebo/vehicle cream (low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [15] RCT **5-armed trial** | 349 people with moderate facial photodamage In review [13] | **Physician-assessed improvement of fine facial wrinkling (6-point scale: 0 = none to 5 = very severe) , 24 weeks** | RR 2.41 95% CI 1.32 to 4.40 | ●●○ | tazarotene 0.01% |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | 27/59 (46%) with tazarotene 0.01% (once-daily application for 24 weeks)<br>11/58 (19%) with vehicle cream (once-daily application for 24 weeks)<br>The remaining arms evaluated tazarotene 0.025%, tazarotene 0.05%, and tazarotene 0.1% once-daily application for 24 weeks | | | |
| [15]<br>RCT<br>**5-armed trial** | 349 people with moderate facial photodamage<br>In review [13] | **Physician-assessed improvement of fine facial wrinkling (6-point scale: 0 = none to 5 = very severe) , 24 weeks**<br>20/58 (34%) with tazarotene 0.025% (once-daily application for 24 weeks)<br>11/58 (19%) with vehicle cream (once-daily application for 24 weeks)<br>The remaining arms evaluated tazarotene 0.01%, tazarotene 0.05%, and tazarotene 0.1% once-daily application for 24 weeks | RR 1.82<br>95% CI 0.96 to 3.45 | ⟷ | Not significant |
| [15]<br>RCT<br>**5-armed trial** | 349 people with moderate facial photodamage<br>In review [13] | **Physician-assessed improvement of fine facial wrinkling (6-point scale: 0 = none to 5 = very severe) , 24 weeks**<br>28/58 (48%) with tazarotene 0.05% (once-daily application for 24 weeks)<br>11/58 (19%) with vehicle cream (once-daily application for 24 weeks)<br>The remaining arms evaluated tazarotene 0.01%, tazarotene 0.025%, and tazarotene 0.1% once-daily application for 24 weeks | RR 2.55<br>95% CI 1.40 to 4.61 | ●●○ | tazarotene 0.05% |
| [15]<br>RCT<br>**5-armed trial** | 349 people with moderate facial photodamage<br>In review [13] | **Physician-assessed improvement of fine facial wrinkling (6-point scale: 0 = none to 5 = very severe) , 24 weeks**<br>32/58 (55%) with tazarotene 0.1% (once-daily application for 24 weeks)<br>11/58 (19%) with vehicle cream (once-daily application for 24 weeks)<br>The remaining arms evaluated tazarotene 0.01%, tazarotene 0.025%, and tazarotene 0.05% once-daily application for 24 weeks | RR 2.91<br>95% CI 1.63 to 5.20 | ●●○ | tazarotene 0.1% |
| [14]<br>RCT | 563 adults with Fitzpatrick skin types I–IV, double blind | **Proportion of people with improved fine wrinkling by at least 1 grade on a 5-point scale , 24 weeks**<br>about 42% with tazarotene 0.1% (applied once-daily for 24 weeks) | P <0.001 | ○○○ | tazarotene 0.1% |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | about 18% with placebo cream (applied once-daily for 24 weeks)<br>Absolute results reported graphically | | | |
| **Improvement in coarse wrinkles** | | | | | |
| [14]<br>RCT | 563 adults with Fitzpatrick skin types I–IV, double blind | **Proportion of people with improved coarse wrinkling by at least 1 grade on a 5-point scale , 24 weeks**<br>about 15% with tazarotene 0.1% (applied once-daily for 24 weeks)<br>about 8% with placebo cream (applied once-daily for 24 weeks)<br>Absolute results reported graphically | P <0.001 | ○○○ | tazarotene 0.1% |

## Quality of life

No data from the following reference on this outcome. [13] [14] [15]

## Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [15]<br>RCT<br>**5-armed trial** | 349 people with moderate facial photodamage<br>In review [13] | **Adverse effects**<br>with tazarotene 0.01% (once-daily application for 24 weeks)<br>with tazarotene 0.025% (once-daily application for 24 weeks)<br>with tazarotene 0.05% (once-daily application for 24 weeks)<br>with tazarotene 0.1% (once-daily application for 24 weeks)<br>with vehicle cream (once-daily application for 24 weeks)<br>Most people reported adverse effects (249/349 [71%])<br>Most adverse effects were considered to be treatment related; the most frequent were signs and symptoms of local skin irritation, such as mild to moderate desquamation, burning sensation, erythema, pruritus, and dry skin | | | |
| [14]<br>RCT | 563 adults with Fitzpatrick skin types I–IV, double blind | **Desquamation**<br>105/283 (37%) with tazarotene 0.1% (applied once-daily for 24 weeks)<br>8/280 (3%) with placebo cream (applied once-daily for 24 weeks)<br>Adverse effects occurred mainly during the first 2 weeks of treat- | P <0.001 | ○○○ | placebo |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | ment, with the most common being desquamation, erythema, and burning | | | |
| [14] RCT | 563 adults with Fitzpatrick skin types I–IV, double blind | **Erythema** 84/283 (30%) with tazarotene 0.1% (applied once-daily for 24 weeks) 6/280 (2%) with placebo cream (applied once-daily for 24 weeks) Adverse effects occurred mainly during the first 2 weeks of treatment, with the most common being desquamation, erythema, and burning | P <0.001 | ○○○ | placebo |
| [14] RCT | 563 adults with Fitzpatrick skin types I–IV, double blind | **Burning** 82/283 (29%) with tazarotene 0.1% (applied once-daily for 24 weeks) 1/280 (0.4%) with placebo cream (applied once-daily for 24 weeks) Adverse effects occurred mainly during the first 2 weeks of treatment, with the most common being desquamation, erythema, and burning | P <0.001 | ○○○ | placebo |

### Tazarotene versus tretinoin:

We found one systematic review (search date 2002), [13] which identified one RCT, and one additional RCT. [16] Both RCTs compared various concentrations of tazarotene with 0.05% tretinoin.

#### Wrinkle improvement

*Tazarotene compared with tretinoin* We don't know how tazarotene and tretinoin compare at improving wrinkles (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [13] Systematic review | 117 people with moderate skin photodamage Data from 1 RCT 5-armed trial; the remaining arms evaluated tazarotene 0.025%, tazarotene 0.05% and tazarotene 0.1% once-daily application for 24 weeks | **Proportion of people with improved fine facial wrinkles (physician-assessed using a 6-point scale: 0 = none to 5 = very severe) , 24 weeks** 27/59 (46%) with tazarotene 0.01% (applied once-daily for 24 weeks) 32/58 (55%) with tretinoin 0.05% (applied once-daily for 24 weeks) | RR 1.21 95% CI 0.84 to 1.73 | ⟷ | Not significant |
| [13] Systematic review | 117 people with moderate skin photodamage Data from 1 RCT 5-armed trial; the remaining arms | **Proportion of people with improved fine facial wrinkles (physician-assessed using a 6-point scale: 0 = none to 5 = very severe) , 24 weeks** | RR 1.60 95% CI 1.05 to 2.44 | ●○○ | tretinoin 0.05% |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | evaluated tazarotene 0.01%, tazarotene 0.05% and tazarotene 0.1% once-daily application for 24 weeks | 20/58 (34%) with tazarotene 0.025% (applied once-daily for 24 weeks)<br>32/58 (55%) with tretinoin 0.05% (applied once-daily for 24 weeks) | | | |
| [13]<br>Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed trial; the remaining arms evaluated tazarotene 0.01%, tazarotene 0.025% and tazarotene 0.1% once-daily application for 24 weeks | **Proportion of people with improved fine facial wrinkles (physician-assessed using a 6-point scale: 0 = none to 5 = very severe) , 24 weeks**<br>28/58 (48%) with tazarotene 0.05% (applied once-daily for 24 weeks)<br>32/58 (55%) with tretinoin 0.05% (applied once-daily for 24 weeks) | RR 1.14<br>95% CI 0.80 to 1.63 | ⟷ | Not significant |
| [13]<br>Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed trial; the remaining arms evaluated tazarotene 0.01%, tazarotene 0.025% and tazarotene 0.05% once-daily application for 24 weeks | **Proportion of people with improved fine facial wrinkles (physician-assessed using a 6-point scale: 0 = none to 5 = very severe) , 24 weeks**<br>32/58 (55%) with tazarotene 0.1% (applied once-daily for 24 weeks)<br>32/58 (55%) with tretinoin 0.05% (applied once-daily for 24 weeks) | RR 1.00<br>95% CI 0.72 to 1.39 | ⟷ | Not significant |
| [16]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Proportion of people with improved fine wrinkling by at least 1 grade on a 5-point scale , 24 weeks**<br>70/88 (80%) with tazarotene 0.1% (applied once-daily in the evening for 24 weeks)<br>53/85 (62%) with tretinoin 0.05% (applied once-daily in the evening for 24 weeks) | P <0.01 | ○○○ | tazarotene 0.1% |
| **Improvement in coarse wrinkles** | | | | | |
| [16]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Proportion of people with improved coarse wrinkling by at least 1 grade on a 5-point scale , 24 weeks**<br>34/88 (39%) with tazarotene 0.1% (applied once-daily in the evening for 24 weeks)<br>29/85 (32%) with tretinoin 0.05% (applied once-daily in the evening for 24 weeks) | P <0.05 | ○○○ | tazarotene 0.1% |

## Quality of life

No data from the following reference on this outcome. [13] [16]

## Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [13]<br>Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed trial; the remaining arms evaluated tazarotene 0.025%, tazarotene 0.05%, and tazarotene 0.1% once-daily application for 24 weeks | **Adverse effects (overall)**<br>2/58 (3%) with tazarotene 0.01% (applied once-daily for 24 weeks)<br>3/58 (5%) with tretinoin 0.05% (applied once-daily for 24 weeks)<br>Skin irritation, burning, peeling, dryness, erythema, and itching were the most common adverse effects with both tazarotene and tretinoin | RR 1.50<br>95% CI 0.26 to 8.65 | ⟷ | Not significant |
| [13]<br>Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed trial; the remaining arms evaluated tazarotene 0.01%, tazarotene 0.05%, and tazarotene 0.1% once-daily application for 24 weeks | **Adverse effects**<br>0/58 (0%) with tazarotene 0.025% (applied once-daily for 24 weeks)<br>3/58 (5%) with tretinoin 0.05% (applied once-daily for 24 weeks)<br>Skin irritation, burning, peeling, dryness, erythema, and itching were the most common adverse effects with both tazarotene and tretinoin | RR 7.0<br>95% CI 0.37 to 132.56 | ⟷ | Not significant |
| [13]<br>Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed trial; the remaining arms evaluated tazarotene 0.025%, tazarotene 0.01%, and tazarotene 0.1% once-daily application for 24 weeks | **Adverse effects**<br>2/58 (3%) with tazarotene 0.05% (applied once-daily for 24 weeks)<br>3/58 (5%) with tretinoin 0.05% (applied once-daily for 24 weeks)<br>Skin irritation, burning, peeling, dryness, erythema, and itching were the most common adverse effects with both tazarotene and tretinoin | RR 1.50<br>95% CI 0.26 to 8.65 | ⟷ | Not significant |
| [13]<br>Systematic review | 117 people with moderate skin photodamage<br>Data from 1 RCT<br>5-armed trial; the remaining arms evaluated tazarotene 0.025%, tazarotene 0.05%, and tazarotene 0.01% once-daily application for 24 weeks | **Adverse effects**<br>2/58 (3%) with tazarotene 0.1% (applied once-daily for 24 weeks)<br>3/58 (5%) with tretinoin 0.05% (applied once-daily for 24 weeks)<br>Skin irritation, burning, peeling, dryness, erythema, and itching were the most common adverse effects with both tazarotene and tretinoin | RR 1.50<br>95% CI 0.26 to 8.65 | ⟷ | Not significant |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [16]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Sensation of burning on the skin**<br>15% with tazarotene 0.1% (applied once-daily in the evening for 24 weeks)<br>0% with tretinoin 0.05% (applied once-daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and occurred most frequently in the first week of treatment | Reported as significant<br>P value not reported | ○○○ | tretinoin |
| [16]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Irritation**<br>21% with tazarotene 0.1% (applied once-daily in the evening for 24 weeks)<br>35% with tretinoin 0.05% (applied once-daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and occurred most frequently in the first week of treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [16]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Dryness**<br>9% with tazarotene 0.1% (applied once-daily in the evening for 24 weeks)<br>15% with tretinoin 0.05% (applied once-daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and occurred most frequently in the first week of treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [16]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Peeling**<br>12% with tazarotene 0.1% (applied once-daily in the evening for 24 weeks)<br>11% with tretinoin 0.05% (applied once-daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and occurred most frequently in the first week of treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [16]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Redness**<br>10% with tazarotene 0.1% (applied once-daily in the evening for 24 weeks)<br>7% with tretinoin 0.05% (applied once-daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and oc- | Reported as not significant<br>P value not reported | ⟷ | Not significant |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | curred most frequently in the first week of treatment | | | |
| [16]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Erythema**<br>3% with tazarotene 0.1% (applied once-daily in the evening for 24 weeks)<br>4% with tretinoin 0.05% (applied once-daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and occurred most frequently in the first week of treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [16]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Stinging**<br>3% with tazarotene 0.1% (applied once-daily in the evening for 24 weeks)<br>6% with tretinoin 0.05% (applied once-daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and occurred most frequently in the first week of treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [16]<br>RCT | 173 people, mean age 55 years, with Fitzpatrick skin types I–IV | **Itching**<br>3% with tazarotene 0.1% (applied once-daily in the evening for 24 weeks)<br>4% with tretinoin 0.05% (applied once-daily in the evening for 24 weeks)<br>Absolute numbers not reported<br>Adverse effects were all of mild to moderate severity, and occurred most frequently in the first week of treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |

**Comment:** None.

## OPTION TRETINOIN

- For GRADE evaluation of interventions for Wrinkles, see table, p 46 .
- Topical tretinoin may improve fine wrinkles when applied daily, compared with vehicle cream, in people with mild to severe photodamage, but its effect on coarse wrinkles is unclear.
- Topical tretinoin may cause itching, burning, erythema, and skin peeling.

## Benefits and harms

### Tretinoin versus vehicle cream:

We found one systematic review (search date 2002), [13] which identified 12 RCTs that separately compared the effects of various concentrations of tretinoin (0.1%, 0.05%, 0.025%, 0.02%, 0.01%, and 0.001%) with vehicle cream. We also found one subsequent RCT. [17]

#### Wrinkle improvement

*Tretinoin compared with vehicle cream* Daily application of tretinoin at a concentration of 0.02% or above may be more effective than vehicle cream at improving fine and coarse facial wrinkles at 16 to 48 weeks in people with mild to severe photodamage. However, daily application of tretinoin at concentrations lower than 0.02% (0.001%–0.01%) may be no more effective than vehicle cream at improving wrinkles (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles (tretinoin 0.001%)** | | | | | |
| [13] Systematic review | 147 people with mild to moderate photodamage<br>Data from 1 RCT | **Proportion of people with improved fine facial wrinkles (physician-assessed) , 24 weeks**<br>20/75 (27%) with topical tretinoin 0.001% (once-daily for 24 weeks)<br>28/72 (39%) with vehicle cream (once-daily for 24 weeks) | RR 0.69<br>95% CI 0.43 to 1.10<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ⟷ | Not significant |
| **Improvement in fine wrinkles (tretinoin 0.01%)** | | | | | |
| [13] Systematic review | 345 people with mild to moderate photodamage<br>3 RCTs in this analysis | **Proportion of people with improved fine facial wrinkles (physician-assessed) , 24 weeks**<br>93/174 (53%) with topical tretinoin 0.01% (once-daily for 24 weeks)<br>63/171 (37%) with vehicle cream (once-daily for 24 weeks) | RR 1.57<br>95% CI 0.91 to 2.71<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ⟷ | Not significant |
| [13] Systematic review | 34 people with mild to moderate photodamage of the face and forearms<br>Data from 1 RCT<br>Within-participant comparison (opposite arms) | **Proportion of people with improved fine forearm wrinkles (physician-assessed) , 24 weeks**<br>24/34 (71%) with topical tretinoin 0.01% (once-daily for 24 weeks)<br>1/34 (3%) with vehicle cream (once-daily for 24 weeks)<br>People were randomised to use tretinoin on either their right or their left forearm, and vehicle cream on the other arm | P <0.01<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ○○○ | tretinoin 0.01% |
| **Improvement in fine wrinkles (tretinoin 0.02%)** | | | | | |
| [13] Systematic review | 328 people with moderate to severe photodamage<br>2 RCTs in this analysis | **Proportion of people with improved fine facial wrinkles (physician-assessed) , 24 weeks**<br>98/159 (62%) with topical tretinoin 0.02% (once-daily for 24 weeks)<br>65/169 (39%) with vehicle cream (once-daily for 24 weeks) | RR 1.60<br>95% CI 1.28 to 2.01<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ●○○ | tretinoin 0.02% |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles (tretinoin 0.025%)** | | | | | |
| [13] Systematic review | 67 people with moderate to severe photodamage<br>Data from 1 RCT | **Mean improvement in fine facial wrinkle score (physician-assessed using a 10-point scale) , 48 weeks**<br>1.3 with topical tretinoin 0.025% (once-daily for 48 weeks)<br>0.6 with vehicle cream (once-daily for 48 weeks) | WMD 0.75<br>95% CI 0.22 to 1.28<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ○○○ | tretinoin 0.025% |
| **Improvement in fine wrinkles (tretinoin 0.05%)** | | | | | |
| [13] Systematic review | 593 people with mild to moderate photodamage<br>5 RCTs in this analysis | **Proportion of people with improved fine facial wrinkles , 24 weeks**<br>186/298 (62%) with topical tretinoin 0.05% (once-daily for 24 weeks)<br>102/295 (35%) with vehicle cream (once-daily for 24 weeks) | RR 1.76<br>95% CI 1.47 to 2.12<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ●○○ | tretinoin 0.05% |
| [13] Systematic review | 125 people with mild to moderate photodamage<br>Data from 1 RCT | **Proportion of people with improved fine forearm wrinkles (physician-assessed) , 24 weeks**<br>32/62 (52%) with topical tretinoin 0.05% (once-daily for 24 weeks)<br>22/63 (35%) with vehicle cream (once-daily for 24 weeks) | RR 1.48<br>95% CI 0.98 to 2.24<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ⟷ | Not significant |
| **Improvement in fine wrinkles (tretinoin 0.1%)** | | | | | |
| [13] Systematic review | 30 people with photodamage of the face and forearms<br>Data from 1 RCT | **Proportion of people with improved fine facial wrinkles (physician-assessed) , 16 weeks**<br>14/15 (93%) with topical tretinoin 0.1% (once-daily for 16 weeks)<br>0/15 (0%) with vehicle cream (once-daily for 16 weeks) | RR 29.00<br>95% CI 1.89 to 445.86<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ●●● | tretinoin 0.1% |
| [13] Systematic review | 30 people<br>Data from 1 RCT | **Proportion of people with improved fine forearm wrinkles , 16 weeks**<br>30/30 (100%) with topical tretinoin 0.1% (once-daily for 16 weeks)<br>0/30 (0%) with vehicle cream (once-daily for 16 weeks)<br>Within-participant comparison (opposite arms)<br>People were randomised to use tretinoin on either their right or their left forearm, and vehicle cream on the other arm | P <0.001<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ○○○ | tretinoin 0.1% |
| [17] RCT | 45 people with moderate to severe facial photodamage | **Proportion of people with improved fine facial wrinkles (physician- and patient-assessed) , 6 months**<br>94% with tretinoin 0.1% (microsphere gel preparation; applied once-daily for 6 months)<br>23% with vehicle gel (applied once-daily for 6 months) | P <0.0001<br>Method of randomisation and allocation concealment were unclear | ○○○ | tretinoin 0.1% |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | Absolute numbers not reported | | | |
| **Improvement in coarse wrinkles (tretinoin 0.01%)** | | | | | |
| [13] Systematic review | 34 people with mild to moderate photodamage of the face and forearms<br>Data from 1 RCT | **Proportion of people with improved coarse facial wrinkles (physician-assessed) , 24 weeks**<br>7/17 (41%) with topical tretinoin 0.01% (once-daily for 24 weeks)<br>1/17 (6%) with vehicle cream (once-daily for 24 weeks) | RR 7.00<br>95% CI 0.96 to 50.93<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ⟷ | Not significant |
| **Improvement in coarse wrinkles (tretinoin 0.02%)** | | | | | |
| [13] Systematic review | 328 people with moderate to severe photodamage<br>2 RCTs in this analysis | **Proportion of people with improved coarse facial wrinkles (physician-assessed) , 24 weeks**<br>64/159 (40%) with topical tretinoin 0.02% (once-daily for 24 weeks)<br>40/169 (24%) with vehicle cream (once-daily for 24 weeks) | RR 1.70<br>95% CI 1.22 to 2.37<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ●○○ | tretinoin 0.02% |
| **Improvement in coarse wrinkles (tretinoin 0.05%)** | | | | | |
| [13] Systematic review | 162 people with mild to moderate photodamage<br>2 RCTs in this analysis | **Proportion of people with improved coarse facial wrinkles (physician-assessed) , 24 weeks**<br>41/79 (52%) with topical tretinoin 0.05% (once-daily for 24 weeks)<br>25/83 (30%) with vehicle cream (once-daily for 24 weeks) | RR 1.68<br>95% CI 1.17 to 2.42<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ●○○ | tretinoin 0.05% |
| **Improvement in coarse wrinkles (tretinoin 0.1%)** | | | | | |
| [13] Systematic review | 30 people with mild to moderate photodamage of the face and forearms<br>Data from 1 RCT | **Proportion of people with improved coarse facial wrinkles (physician-assessed) , 16 weeks**<br>6/15 (40%) with topical tretinoin 0.1% (once-daily for 16 weeks)<br>0/15 (0%) with vehicle cream (once-daily for 16 weeks) | RR 13.0<br>95% CI 0.80 to 212.02<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ⟷ | Not significant |
| [13] Systematic review | 30 people<br>Data from 1 RCT | **Proportion of people with improved coarse forearm wrinkles , 16 weeks**<br>9/30 (30%) with topical tretinoin 0.1% (once-daily for 16 weeks)<br>0/30 (0%) with vehicle cream (once-daily for 16 weeks)<br>Within-participant comparison (opposite arms)<br>People were randomised to use tretinoin on either their right or their left forearm, and vehicle cream on the other arm | P <0.01<br>RCTs identified by review had methodological limitations; see Further information on studies for full details | ○○○ | tretinoin 0.1% |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [17]<br>RCT | 45 people with moderate to severe facial photodamage | **Proportion of people with improved coarse facial wrinkles (physician- and patient-assessed) , 6 months**<br>22% with tretinoin 0.1% (microsphere gel preparation; applied once-daily for 6 months)<br>5% with vehicle gel (applied once-daily for 6 months)<br>Absolute numbers not reported | P = 0.1<br>Method of randomisation and allocation concealment were unclear | ⟷ | Not significant |
| **Improvement in wrinkles (global; tretinoin 0.1%)** | | | | | |
| [17]<br>RCT | 45 people with moderate to severe facial photodamage | **Global assessment score (investigators and participants scored signs of photodamage and skin irritation, using a scale from 0–9 [0 = none, 1–3 = mild, 4–6 = moderate, 7–9 = severe]) , 6 months**<br>with tretinoin 0.1% (microsphere gel preparation; applied once-daily for 6 months)<br>with vehicle gel (applied once-daily for 6 months)<br>Absolute results reported graphically<br>The RCT reported a significant increase in the proportion of people improved with tretinoin compared with vehicle gel | P <0.0003<br>Method of randomisation and allocation concealment were unclear | ○○○ | tretinoin 0.1% |
| [17]<br>RCT | 45 people with moderate to severe facial photodamage | **Proportion of people with improved facial tactile roughness (physician- and patient-assessed) , 6 months**<br>83% with tretinoin 0.1% (microsphere gel preparation; applied once-daily for 6 months)<br>91% with vehicle gel (applied once-daily for 6 months)<br>Absolute numbers not reported | P = 0.53<br>Method of randomisation and allocation concealment were unclear | ⟷ | Not significant |

## Quality of life

No data from the following reference on this outcome. [13] [17]

## Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects (tretinoin 0.01%)** | | | | | |
| [13]<br>Systematic review | 344 people with mild to moderate photodamage<br>2 RCTs in this analysis | **Burning or stinging , 24 weeks**<br>36/173 (21%) with topical tretinoin 0.01% (once-daily for 24 weeks) | RR 1.99<br>95% CI 1.20 to 3.32 | ●○○ | vehicle cream |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | 18/171 (11%) with vehicle cream (once-daily for 24 weeks)<br>See Further information on studies for details on most common adverse effects associated with tretinoin | | | |
| **Adverse effects (tretinoin 0.05%)** | | | | | |
| [13]<br>Systematic review | 349 people<br>2 RCTs in this analysis | **Erythema , 24 weeks**<br>60/178 (34%) with topical tretinoin 0.05% (once-daily for 24 weeks)<br>16/171 (9%) with vehicle cream (once-daily for 24 weeks)<br>See Further information on studies for details on most common adverse effects associated with tretinoin | RR 3.58<br>95% CI 1.99 to 6.46 | ●●○ | vehicle cream |
| [13]<br>Systematic review | 349 people<br>2 RCTs in this analysis | **Scaling/dryness , 24 weeks**<br>115/178 (65%) with topical tretinoin 0.05% (once-daily for 24 weeks)<br>49/171 (29%) with vehicle cream (once-daily for 24 weeks)<br>See Further information on studies for details on most common adverse effects associated with tretinoin | RR 2.23<br>95% CI 1.72 to 2.88 | ●●○ | vehicle cream |
| [13]<br>Systematic review | 349 people<br>2 RCTs in this analysis | **Burning and stinging , 24 weeks**<br>69/178 (39%) with topical tretinoin 0.05% (once-daily for 24 weeks)<br>18/171 (11%) with vehicle cream (once-daily for 24 weeks)<br>See Further information on studies for details on most common adverse effects associated with tretinoin | RR 3.75<br>95% CI 2.35 to 5.98 | ●●○ | vehicle cream |
| **Adverse effects (tretinoin 0.1%)** | | | | | |
| [13]<br>Systematic review | 76 people with moderate to severe photodamage of the face and forearms<br>Data from 1 RCT | **Erythema , 48 weeks**<br>16/36 (44%) with topical tretinoin 0.1% (once-daily for 48 weeks)<br>0/40 (0%) with vehicle cream (once-daily for 48 weeks)<br>See Further information on studies for details on most common adverse effects associated with tretinoin | RR 36.57<br>95% CI 2.27 to 588.35 | ●●● | vehicle cream |
| [17]<br>RCT | 45 people with moderate to severe facial photodamage | **Skin erythema , 1 month**<br>with tretinoin 0.1% (microsphere gel preparation; applied once-daily for 6 months)<br>with vehicle gel (applied once-daily for 6 months)<br>Absolute results not reported | P = 0.0005<br>Method of randomisation and allocation concealment were unclear | ○○○ | vehicle gel |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | RCT reported that tretinoin increased the severity of skin erythema compared with vehicle gel | | | |
| [17]<br>RCT | 45 people with moderate to severe facial photodamage | **Peeling , 1 month**<br>with tretinoin 0.1% (microsphere gel preparation; applied once-daily for 6 months)<br>with vehicle gel (applied once-daily for 6 months)<br>Absolute results not reported<br>RCT reported that tretinoin increased the severity of peeling compared with vehicle gel | P <0.0001<br>Method of randomisation and allocation concealment were unclear | | vehicle gel |
| [17]<br>RCT | 45 people with moderate to severe facial photodamage | **Dryness , 1 month**<br>with tretinoin 0.1% (microsphere gel preparation; applied once-daily for 6 months)<br>with vehicle gel (applied once-daily for 6 months)<br>Absolute results not reported<br>RCT reported that tretinoin increased the severity of dryness compared with vehicle gel | P <0.0001<br>Method of randomisation and allocation concealment were unclear | | vehicle gel |
| [17]<br>RCT | 45 people with moderate to severe facial photodamage | **Itching , 1 month**<br>with tretinoin 0.1% (microsphere gel preparation; applied once-daily for 6 months)<br>with vehicle gel (applied once-daily for 6 months)<br>Absolute results not reported<br>RCT reported that tretinoin increased the severity of itching compared with vehicle gel | P = 0.0005<br>Method of randomisation and allocation concealment were unclear | | vehicle gel |
| [17]<br>RCT | 45 people with moderate to severe facial photodamage | **Burning/stinging , 1 month**<br>with tretinoin 0.1% (microsphere gel preparation; applied once-daily for 6 months)<br>with vehicle gel (applied once-daily for 6 months)<br>Absolute results not reported<br>RCT reported that tretinoin increased the severity of burning/stinging compared with vehicle gel | P <0.0001<br>Method of randomisation and allocation concealment were unclear | | vehicle gel |
| [17]<br>RCT | 45 people with moderate to severe facial photodamage | **Peeling , 6 months**<br>with tretinoin 0.1% (microsphere gel preparation; applied once-daily for 6 months)<br>with vehicle gel (applied once-daily for 6 months)<br>Absolute results not reported<br>RCT reported that tretinoin increased the severity of peeling compared with vehicle gel | P = 0.001<br>Method of randomisation and allocation concealment were unclear | | vehicle gel |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [17]<br>RCT | 45 people with moderate to severe facial photodamage | **Dryness , 6 months**<br>with tretinoin 0.1% (microsphere gel preparation; applied once-daily for 6 months)<br>with vehicle gel (applied once-daily for 6 months)<br>Absolute results not reported<br>RCT reported that tretinoin increased the severity of dryness compared with vehicle gel | P = 0.007<br>Method of randomisation and allocation concealment were unclear | ○○○ | vehicle gel |

**Tretinoin versus tazarotene:**

See option on Tazarotene, p 3 .

**Further information on studies**

[13] Methodological limitations: The RCTs included in the systematic review are limited by their small sample sizes, short durations, and inconsistencies among investigator and participant assessments. The methods of randomisation and allocation concealment were unclear in most RCTs in the systematic review. Adverse effects of tretinoin: the systematic review found that all strengths of tretinoin were associated with adverse effects. The most common adverse effects were itching, burning/stinging, dryness, and erythema, which peaked during the first 2 weeks and decreased with time.

**Comment:** We found individual case reports of congenital defects associated with topical tretinoin used during the first trimester of pregnancy. [18] [19] We found one observational study that identified 215 case histories of women who used tretinoin cream for acne during the first trimester of pregnancy, and compared them with 430 age-matched, non-exposed women who delivered infants at the same hospital. [20] The study found no significant difference in the incidence of major congenital disorders (1.9% with tretinoin *v* 2.6% with control; RR 0.7, 95% CI 0.2 to 2.3).

## OPTION ISOTRETINOIN

- For GRADE evaluation of interventions for Wrinkles, see table, p 46 .
- Isotretinoin cream applied daily may improve fine and coarse wrinkles compared with vehicle cream in people with mild to severe photodamage, but may cause severe irritation of the face.
- Isotretinoin is associated with increased facial erythema, scaling/dryness, and burning/stinging compared with vehicle cream.

## Benefits and harms

**Isotretinoin versus vehicle cream:**

We found one systematic review (search date 2002), [13] which included one RCT comparing isotretinoin with vehicle cream. We also found one additional RCT. [21]

**Wrinkle improvement**

*Isotretinoin compared with vehicle cream* Isotretinoin cream applied daily may be more effective than vehicle cream at improving fine and coarse facial wrinkles and forearm wrinkles after 36 weeks in people with mild to severe photodamage (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [13]<br>Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodamage of arms and hands<br>Data from 1 RCT | **Improvement in fine facial wrinkles , 36 weeks**<br>with topical isotretinoin 0.1% (0.5 g) (applied once-daily for 36 weeks)<br>with vehicle cream (applied once-daily for 36 weeks) | WMD 4.90<br>95% CI 3.79 to 6.01 | ○○○ | isotretinoin 0.1% |
| [13]<br>Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodamage of arms and hands<br>Data from 1 RCT | **Improvement in fine wrinkles of the forearm , 36 weeks**<br>with topical isotretinoin 0.1% (0.5 g) (applied once-daily for 36 weeks)<br>with vehicle cream (applied once-daily for 36 weeks) | WMD 3.0<br>95% CI 2.17 to 3.83 | ○○○ | isotretinoin 0.1% |
| [21]<br>RCT | 776 people in 17 US centres, aged 20–76 years, with mild to moderate facial photodamage | **Physician-assessed improvement of fine facial wrinkling (change from baseline measured on 100 mm VAS: –50 = worse, 0 = no change, +50 = better) , 36 weeks**<br>+7.4 with topical isotretinoin 0.05% (applied once-daily for 12 weeks), followed by isotretinoin 0.01% (applied for the next 24 weeks)<br>+5.3 with vehicle cream (applied for 36 weeks)<br>Analysis of 613 people (79%) at 36 weeks; analysis was not by intention to treat<br>Change in fine wrinkles was also assessed by 5 dermatologists; see Further information on studies for details of findings | P <0.01 | ○○○ | isotretinoin |
| [21]<br>RCT | 776 people in 17 US centres, aged 20–76 years, with mild to moderate facial photodamage | **Participant-assessed improvement of fine facial wrinkling (change from baseline measured on 100 mm VAS: –50 = worse, 0 = no change, +50 = better) , 36 weeks**<br>+11.7 with topical isotretinoin 0.05% (applied once-daily for 12 weeks), followed by isotretinoin 0.01% (applied daily for the next 24 weeks)<br>+7.9 with vehicle cream (applied for 36 weeks)<br>Analysis of 613 people (79%) at 36 weeks; analysis was not by intention to treat<br>Change in fine wrinkles was also assessed by 5 dermatologists; see Further information on studies for details of findings | P <0.01 | ○○○ | isotretinoin |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in coarse wrinkles** | | | | | |
| [13] Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodamage of arms and hands<br>Data from 1 RCT | **Improvement in coarse facial wrinkles , 36 weeks**<br>with topical isotretinoin 0.1% (0.5 g) (applied once-daily for 36 weeks)<br>with vehicle cream (applied once-daily for 36 weeks) | WMD 3.0<br>95% CI 2.17 to 3.83 | ○○○ | isotretinoin 0.1% |
| **Improvement in wrinkles (global)** | | | | | |
| [21] RCT | 776 people in 17 US centres, aged 20–76 years, with mild to moderate facial photodamage | **Physician-assessed overall skin appearance (change from baseline measured on 100 mm VAS: –50 = worse, 0 = no change, +50 = better) , 36 weeks**<br>+8.3 with topical isotretinoin 0.05% (applied once-daily for 12 weeks), followed by isotretinoin 0.01% (applied for the next 24 weeks)<br>+6.4 with vehicle cream (applied for 36 weeks)<br>Analysis of 613 people (79%) at 36 weeks; analysis was not by intention to treat | P <0.01 | ○○○ | isotretinoin |
| [21] RCT | 776 people in 17 US centres, aged 20–76 years, with mild to moderate facial photodamage | **Participant-assessed overall skin appearance (change from baseline measured on 100 mm VAS: –50 = worse, 0 = no change, +50 = better) , 36 weeks**<br>with topical isotretinoin 0.05% (applied once-daily for 12 weeks), followed by isotretinoin 0.01% (applied for the next 24 weeks)<br>with vehicle cream (applied for 36 weeks)<br>Analysis of 613 people (79%) at 36 weeks; analysis was not by intention to treat | Reported as not significant<br>P value not reported | ⟷ | Not significant |

## Quality of life

No data from the following reference on this outcome. [13] [21]

## Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [13] Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodam- | **Withdrawal because of adverse effects**<br>25/323 (8%) with topical isotretinoin 0.1% (0.5 g; applied once-daily for 36 weeks) | Significance not assessed | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | age of arms and hands<br>Data from 1 RCT | 9/353 (3%) with vehicle cream (applied once daily for 36 weeks) | | | |
| [13]<br>Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodamage of arms and hands<br>Data from 1 RCT | **Erythema**<br>210/323 (65%) with topical isotretinoin 0.1% (0.5 g; applied once-daily for 36 weeks)<br>90/358 (25%) with vehicle cream (applied once daily for 36 weeks) | RR 2.59<br>95% CI 2.13 to 3.15 | ●●○ | vehicle cream |
| [13]<br>Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodamage of arms and hands<br>Data from 1 RCT | **Scaling/dryness**<br>175/323 (54%) with topical isotretinoin 0.1% (0.5 g; applied once-daily for 36 weeks)<br>30/358 (8%) with vehicle cream (applied once daily for 36 weeks) | RR 6.47<br>95% CI 4.52 to 9.24 | ●●● | vehicle cream |
| [13]<br>Systematic review | 681 people with moderate to severe facial photodamage, and mild to severe photodamage of arms and hands<br>Data from 1 RCT | **Burning/stinging**<br>214/323 (66%) with topical isotretinoin 0.1% (0.5 g; applied once-daily for 36 weeks)<br>55/358 (15%) with vehicle cream (applied once daily for 36 weeks) | RR 4.31<br>95% CI 3.34 to 5.57 | ●●○ | vehicle cream |
| [21]<br>RCT | 776 people in 17 US centres, aged 20–76 years, with mild to moderate facial photodamage | **Withdrawal because of adverse effects**<br>5/307 (1.6%) with topical isotretinoin 0.05% (applied once-daily for 12 weeks), followed by isotretinoin 0.01% (applied for the next 24 weeks)<br>1/306 (0.3%) with vehicle cream (applied for 36 weeks)<br>The RCT reported that severe intolerability reactions, which were unspecified, occurred in "less than 5% of people" taking isotretinoin | Significance not assessed | | |

**Further information on studies**

[21] Five dermatologists assessed pre- and post-treatment photographs. The RCT reported that all dermatologists found that isotretinoin significantly improved fine wrinkles compared with vehicle cream (P <0.05).

**Comment:** The RCTs provide limited evidence on the effectiveness of isotretinoin in the treatment of wrinkles, and so more studies are needed to confirm these findings.

## OPTION CHEMICAL PEEL (INCLUDING ALPHA AND BETA HYDROXYL ACIDS)

- For GRADE evaluation of interventions for Wrinkles, see table, p 46 .

- We don't know whether chemical peel (including alpha and beta hydroxyl acids) is beneficial in treating wrinkles as we found insufficient evidence.

## Benefits and harms

### Glycolic acid versus vehicle cream:

We found one systematic review (search date 2002), [13] which identifed two RCTs (149 people with mild to moderate photodamage). One RCT evaluated 8% glycolic acid for 22 weeks and the other RCT evaluated 5% glycolic acid for 12 weeks. The systematic review did not perform a meta-analysis.

#### Wrinkle improvement

*Glycolic acid compared with vehicle cream* Glycolic acid may be more effective than vehicle cream at improving fine wrinkles at 22 weeks, but we don't know whether it is more effective at 12 weeks (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [13] Systematic review | 75 people<br>Data from 1 RCT | **Improvement in fine wrinkles , 12 weeks**<br>with glycolic acid 5% (applied for 12 weeks)<br>with vehicle cream (applied for 12 weeks)<br>Initially, creams were applied once every 2 days; if there was no irritation after the first week, creams were applied once-daily, and then, after 2 weeks, twice-daily | WMD –0.42<br>95% CI –1.68 to +0.84 | ⟷ | Not significant |
| [22] RCT **3-armed trial** | 74 women<br>In review [13] | **Physician-assessed improvement of fine facial wrinkling (measured on a 10-point scale: 0 = none and 9 = severe) , 22 weeks**<br>22% with glycolic acid 8% (applied twice-daily)<br>15% with vehicle cream (applied twice-daily)<br>The remaining arm evaluated lactic acid 8% applied twice-daily | P <0.05 | ○○○ | glycolic acid 8% |
| [22] RCT **3-armed trial** | 74 women<br>In review [13] | **Mean grade change of physician-assessed fine facial wrinkling (measured on a 10-point scale: 0 = none and 9 = severe) , 22 weeks**<br>–1.14 with glycolic acid 8% (applied twice-daily)<br>–0.86 with vehicle cream (applied twice-daily)<br>The remaining arm evaluated lactic acid 8% applied twice-daily | P <0.05 | ○○○ | glycolic acid 8% |

#### Quality of life

No data from the following reference on this outcome. [13] [22]

#### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [13]<br>Systematic review | 75 people<br>Data from 1 RCT | **Adverse effects**<br>with glycolic acid 5% (applied twice-daily)<br>with vehicle cream (applied twice-daily)<br>No major adverse effects or complications were associated with glycolic acid 5% | | | |
| [22]<br>RCT<br>**3-armed trial** | 74 women<br>In review [13] | **Adverse effects**<br>with glycolic acid 8% (applied twice-daily)<br>with lactic acid 8% (applied twice-daily)<br>with vehicle cream (applied twice-daily)<br>30% of people had some degree of erythema at one or more treatment sites | | | |

### Lactic acid versus vehicle cream:

We found one systematic review (search date 2002), [13] which identified one RCT assessing lactic acid. [22]

#### Wrinkle improvement

*Lactic acid compared with vehicle cream* Lactic acid 8% (applied twice-daily) may be more effective than vehicle cream at improving fine wrinkles at 22 weeks (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in fine wrinkles** | | | | | |
| [22]<br>RCT<br>**3-armed trial** | 74 women<br>In review [13] | **Physician-assessed improvement of fine facial wrinkling (measured on a 10-point scale: 0 = none and 9 = severe) , 22 weeks**<br>22% with lactic acid 8% (applied twice-daily)<br>15% with vehicle cream (applied twice-daily)<br>The remaining arm evaluated glycolic acid 8% applied twice-daily | P <0.05 | ○○○ | lactic acid 8% |
| [22]<br>RCT<br>**3-armed trial** | 74 women<br>In review [13] | **Mean grade change of physician-assessed fine facial wrinkling (measured on a 10-point scale: 0 = none and 9 = severe) , 22 weeks**<br>–1.04 with lactic acid 8% (applied twice-daily)<br>–0.86 with vehicle cream (applied twice-daily)<br>The remaining arm evaluated glycolic acid 8% applied twice-daily | P <0.05 | ○○○ | lactic acid 8% |

### Quality of life

No data from the following reference on this outcome. [13] [22]

### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [22]<br>RCT<br>**3-armed trial** | 74 women<br>In review [13] | **Adverse effects**<br>with glycolic acid 8% (applied twice-daily)<br>with lactic acid 8% (applied twice-daily)<br>with vehicle cream (applied twice-daily)<br>30% of people had some degree of erythema at one or more treatment sites | | | |

**Chemical peel (including alpha and beta hydroxyl acids) versus carbon dioxide laser:**
See option on Carbon dioxide laser, p 23 .

**Comment:** In this option, we have covered all types of chemical peel (alone or a combination of elements); for example, phenol peel (e.g., Baker's phenol, Baker-Gordon peel), trichloroacetic acid, alpha hydroxyl acid (e.g., glycolic acid, lactic acid), beta hydroxyl acid, salicylic acid, retinoic acid, and Jessner peeling. We have reported any studies of sufficient quality that we found.

The effectiveness of glycolic acid and lactic acid in the treatment of wrinkles is based on data from RCTs that reported the mean change in grade as an outcome. However, whether the mean grade change results in a clinically important improvement is not clear. The effects of chemical peels and carbon dioxide lasers are likely to be dependent on the technique of the dermatological surgeon; therefore, results may not generalise to different populations. [13]

## OPTION CARBON DIOXIDE LASER

- For GRADE evaluation of interventions for Wrinkles, see table, p 46 .
- We don't know whether carbon dioxide laser is better than placebo in people with wrinkles, as we found no direct evidence.
- We don't know whether carbon dioxide laser is more effective than dermabrasion, chemical peel, erbium:YAG laser or carbon dioxide laser plus variable pulse erbium:YAG laser at improving wrinkles, as studies have given inconclusive results.
- Adverse effects are common with carbon dioxide laser, especially erythema.

### Benefits and harms

**Carbon dioxide laser versus placebo:**
We found no systematic reviews or RCTs.

### Carbon dioxide laser versus dermabrasion:

We found one systematic review (search date 2002, [13] 3 RCTs, 55 women with wrinkles) comparing carbon dioxide laser with dermabrasion.

#### Wrinkle improvement

*Carbon dioxide laser compared with dermabrasion* We don't know how carbon dioxide laser treatment and dermabrasion compare at improving wrinkles (low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement of wrinkles** | | | | | |
| [13] Systematic review | 55 women with wrinkles<br>3 RCTs in this analysis | **Wrinkle score (on a 0–5 scale)**<br>with carbon dioxide laser<br>with dermabrasion<br>RCT reported that carbon dioxide laser produced a better wrinkle score than dermabrasion but the difference was small | WMD –0.10<br>95% CI –0.35 to +0.16 | ⟷ | Not significant |

#### Quality of life

No data from the following reference on this outcome. [13]

#### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [13] Systematic review | 55 women with wrinkles<br>3 RCTs in this analysis | **Erythema , 1 month**<br>with carbon dioxide laser<br>with dermabrasion<br>See Further information on studies for enhanced reporting from one RCT identified by the review<br>See Further information on studies for information on withdrawal rates | WMD 0.31<br>95% CI 0.15 to 0.47 | ○○○ | dermabrasion |
| [23] RCT | 20 women with wrinkles<br>In review [13] | **Hypertrophic scar**<br>with carbon dioxide laser<br>with dermabrasion<br>One woman developed a hypertrophic scar on the side treated with dermabrasion | | | |
| [23] RCT | 20 women with wrinkles<br>In review [13] | **Herpetic lesions**<br>with carbon dioxide laser<br>with dermabrasion<br>Three people developed herpetic lesions several days after treatment, despite valaciclovir prophylaxis | | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [23]<br>RCT | 20 women with wrinkles<br>In review [13] | **Proportion of people reporting worse 'post-treatment drainage' with each intervention**<br>10/20 (50%) with carbon dioxide laser<br>2/20 (10%) with dermabrasion | P = 0.002 | ○○○ | dermabrasion |

### Carbon dioxide laser versus chemical peel (including alpha and beta hydroxyl acids):

We found one systematic review (search date 2002), [13] which identified one RCT (20 women), [24] and one additional RCT comparing carbon dioxide laser with chemical peel. [25]

#### Wrinkle improvement

*Carbon dioxide laser compared with chemical peel* We don't know how carbon dioxide laser treatment and chemical peel compare at improving wrinkles (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in wrinkles** | | | | | |
| [24]<br>RCT | 20 women, aged 51–71 years, with Fitzpatrick skin type I–III and with wrinkles on upper lip<br>In review [13] | **Average change in upper lip wrinkle score (6-point scale: 0 = none to 5 = severe) , baseline to 6 months**<br>from 4.30 to 1.11 with carbon dioxide laser<br>from 4.20 to 0.47 with Baker's phenol chemical peel<br>The change from baseline was statistically significant for both carbon dioxide laser and chemical peel (P <0.001) | P <0.03 | ○○○ | Baker's phenol chemical peel |
| [25]<br>RCT | 24 men and women, aged 43–73 years, with Fitzpatrick skin types I–III | **Severity of periorbital wrinkles (6-point scale: 0 = none to 5 = severe) , baseline to 6 months**<br>from 4.00 to 1.75 with carbon dioxide laser<br>from 4.13 to 3.29 with trichloroacetic acid chemical peel<br>Within-participant comparison (opposite sides of the face)<br>Investigators and participants were not blinded to treatment allocation, but an independent blinded investigator assessed outcomes | P <0.001 | ○○○ | carbon dioxide laser |

#### Quality of life

No data from the following reference on this outcome. [13] [24] [25]

#### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [24]<br>RCT | 20 women, aged 51–71 years, with Fitzpatrick skin type I–III and with wrinkles on upper lip<br>In review [13] | **Erythema**<br>with carbon dioxide laser<br>with Baker's phenol chemical peel<br>Absolute results not reported<br>55% of people had erythema coagulum on the upper lip or both lips; in 10% of people it was more severe on the laser treated side, and in 35% of people this was more severe on the chemical peel side | | | |
| [24]<br>RCT | 20 women, aged 51–71 years, with Fitzpatrick skin type I–III and with wrinkles on upper lip<br>In review [13] | **Hypertrophic scar**<br>with carbon dioxide laser<br>with Baker's phenol chemical peel<br>One person developed an 8 mm hypertrophic scar on the phenol-treated side | | | |
| [24]<br>RCT | 20 women, aged 51–71 years, with Fitzpatrick skin type I–III and with wrinkles on upper lip<br>In review [13] | **Herpes simplex infection**<br>with carbon dioxide laser<br>with Baker's phenol chemical peel<br>Herpes simplex infection was reported in 3 people, which responded to valaciclovir (treatment side not reported) | | | |
| [25]<br>RCT | 24 men and women, aged 43–73 years, with Fitzpatrick skin types I–III | **Mean length of erythema duration**<br>4.5 months with carbon dioxide laser<br>2.5 months with trichloroacetic acid chemical peel<br>Within-participant comparison (opposite sides of the face) | | | |
| [25]<br>RCT | 24 men and women, aged 43–73 years, with Fitzpatrick skin types I–III | **Scarring**<br>13/24 (52%) with carbon dioxide laser<br>3/24 (13%) with trichloroacetic acid chemical peel<br>Within-participant comparison (opposite sides of the face)<br>All scars improved or resolved after treatment with topical silicone paste or intralesional corticosteroids | | | |
| [25]<br>RCT | 24 men and women, aged 43–73 years, with Fitzpatrick skin types I–III | **Contact dermatitis to bacitracin–polymyxin B ointment**<br>with carbon dioxide laser<br>with trichloroacetic acid chemical peel<br>Within-participant comparison (opposite sides of the face)<br>Symptoms occurred in 4 people; resolved after switching topical | | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | treatment to petrolatum and a low-potency topical corticosteroid | | | |
| [25] RCT | 24 men and women, aged 43–73 years, with Fitzpatrick skin types I–III | **Hypopigmentation** with carbon dioxide laser with trichloroacetic acid chemical peel Within-participant comparison (opposite sides of the face) Hypopigmentation developed in 6/24 (25%) people in the carbon dioxide laser-treated arm, but resolved or improved by the end of the study; no further data reported | | | |
| [25] RCT | 24 men and women, aged 43–73 years, with Fitzpatrick skin types I–III | **Whitehead formation** with carbon dioxide laser with trichloroacetic acid chemical peel Within-participant comparison (opposite sides of the face) Whitehead formation was relatively common during the prolonged healing phase, but resolved or improved with tretinoin or manual extraction (no data reported) | | | |

No data from the following reference on this outcome. [13]

### Carbon dioxide laser versus erbium:YAG laser:

We found one systematic review (search date 2002), [13] which identified three RCTs (55 people) [26] [27] [28] comparing carbon dioxide laser versus erbium:YAG laser. The results of the RCTs were not combined in the systematic review because of the variability in outcomes. We found one subsequent RCT. [29]

#### Wrinkle improvement

*Carbon dioxide laser compared with erbium:YAG laser* We don't know how carbon dioxide laser and erbium:YAG laser compare at improving wrinkles (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in wrinkles** | | | | | |
| [26] RCT | 21 women, aged 39–74 years, with upper lip wrinkles, Fitzpatrick skin types I–IV In review [13] | **Overall wrinkle improvement (not defined) , 2 months** 63% with carbon dioxide laser 54% with variable pulse erbium:YAG laser Within-participant comparison (opposite sides of the upper lip) Investigators and participants were not blinded to treatment allocation, but a blinded panel of plastic surgeons and trained research assistants assessed outcomes Photographs and digital images of participants were recorded pre- | Significance not assessed Results should be interpreted with caution because the participants and investigators were not blinded to treatment allocation | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | operatively and at intervals up to 2 months after treatment | | | |
| [27]<br>RCT | 12 women and 1 man, aged 30–80 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [13] | **Average improvement in wrinkle score (assessed from photographs; 9-point scale: 0 = absent to 8 = severe)**<br>1–2 points with pulsed carbon dioxide laser (one pass)<br>1–2 points with erbium:YAG laser (four passes)<br>Within-participant comparison (opposite sides of the face)<br>Lasers applied to periorbital or perioral sites, or both<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of physicians familiar with laser resurfacing assessed outcomes | Reported as not significant<br>P value not reported<br>The RCT may have been too small to exclude a clinically important difference<br>Results should be interpreted with caution because the participants and investigators were not blinded to treatment allocation | ⟷ | Not significant |
| [28]<br>RCT | 19 women and 2 men, aged 18–90 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [13] | **Wrinkle improvement (measured by aggregate of investigators', participants', and panel's assessments [photographs]) , 6 months**<br>with carbon dioxide laser<br>with variable pulse erbium:YAG laser<br>Absolute results not reported<br>Within-participant comparison (opposite sides of the face)<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of dermatologists also assessed outcomes | P <0.03<br>Results should be interpreted with caution because the participants and investigators were not blinded to treatment allocation | ○○○ | carbon dioxide laser |
| [29]<br>RCT | 28 people with mild to moderate periorbital rhytides ('crow's feet') at rest (Fitzpatrick skin type II – fine to moderate depth wrinkles, moderate number of lines) | **Difference between sides after treatment**<br>with fractional carbon dioxide laser<br>with fractional erbium:YAG laser<br>Absolute results not reported<br>Within-participant comparison (opposite sides of the face)<br>Single treatment on each side of the face only | P = 0.53<br>See Further information on studies | ⟷ | Not significant |
| [29]<br>RCT | 28 people with mild to moderate periorbital rhytides ('crow's feet') at rest (Fitzpatrick skin type II – fine to moderate depth wrinkles, moderate number of lines) | **Side of face rated as 'improved' (not further defined)**<br>64% with fractional carbon dioxide laser<br>57% with fractional erbium:YAG laser<br>Absolute numbers not reported<br>Within-participant comparison (opposite sides of the face)<br>Single treatment on each side of the face only | Significance not reported<br>See Further information on studies | | |

## Quality of life

No data from the following reference on this outcome. [13] [26] [27] [28] [29]

## Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [26]<br>RCT | 21 women, aged 39–74 years, with upper lip wrinkles, Fitzpatrick skin types I–IV<br>In review [13] | **Postoperative erythema**<br>with carbon dioxide laser<br>with variable pulse erbium:YAG laser<br>Within-participant comparison (opposite sides of the upper lip)<br>Postoperative erythema occurred with both treatments<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of plastic surgeons and trained research assistants assessed outcomes<br>Photographs and digital images of participants were recorded preoperatively and at intervals up to 2 months after treatment | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [26]<br>RCT | 21 women, aged 39–74 years, with upper lip wrinkles, Fitzpatrick skin types I–IV<br>In review [13] | **Hyperpigmentation**<br>with carbon dioxide laser<br>with variable pulse erbium:YAG laser<br>Within-participant comparison (opposite sides of the upper lip)<br>1 person had mild hyperpigmentation at about 4 weeks with erbium:YAG laser, which cleared by 3 months<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of plastic surgeons and trained research assistants assessed outcomes<br>Photographs and digital images of participants were recorded preoperatively and at intervals up to 2 months after treatment | | | |
| [27]<br>RCT | 12 women and 1 man, aged 30–80 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [13] | **Postoperative erythema , 2 weeks**<br>with pulsed carbon dioxide laser (1 pass)<br>with erbium:YAG laser (4 passes)<br>Within-participant comparison (opposite sides of the face)<br>Lasers applied to periorbital or perioral sites, or both; investigators and participants were not blinded to treatment allocation, but a blinded panel of physicians | P <0.04 | ○○○ | carbon dioxide laser |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | familiar with laser resurfacing assessed outcomes | | | |
| [27]<br>RCT | 12 women and 1 man, aged 30–80 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [13] | **Postoperative erythema , 2 and 6 months**<br>with pulsed carbon dioxide laser (1 pass)<br>with erbium:YAG laser (4 passes)<br>Within-participant comparison (opposite sides of the face)<br>Rates of postoperative erythema were similar between the 2 groups at 2 and 6 months<br>Lasers applied to periorbital or perioral sites, or both; investigators and participants were not blinded to treatment allocation, but a blinded panel of physicians familiar with laser resurfacing assessed outcomes | | | |
| [27]<br>RCT | 12 women and 1 man, aged 30–80 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [13] | **Hyperpigmentation**<br>with pulsed carbon dioxide laser (1 pass)<br>with erbium:YAG laser (4 passes)<br>Within-participant comparison (opposite sides of the face)<br>Lasers applied to periorbital or perioral sites, or both<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of physicians familiar with laser resurfacing assessed outcomes | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [28]<br>RCT | 19 women and 2 men, aged 18–90 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [13] | **Erythema , 2 weeks**<br>95% with carbon dioxide laser<br>67% with variable pulse erbium:YAG laser<br>Within-participant comparison (opposite sides of the face)<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of dermatologists also assessed outcomes | | | |
| [28]<br>RCT | 19 women and 2 men, aged 18–90 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [13] | **Erythema , 2 months**<br>62% with carbon dioxide laser<br>24% with variable pulse erbium:YAG laser<br>Within-participant comparison (opposite sides of the face)<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of dermatologists also assessed outcomes | | | |
| [28]<br>RCT | 19 women and 2 men, aged 18–90 years, with perioral or periorbital wrin- | **Mild erythema , 6 months**<br>10% with carbon dioxide laser<br>0% with variable pulse erbium:YAG laser | | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | kles, Fitzpatrick skin types I–III<br>In review [13] | Within-participant comparison (opposite sides of the face)<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of dermatologists also assessed outcomes | | | |
| [28]<br>RCT | 19 women and 2 men, aged 18–90 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [13] | **Hypopigmentation**<br>43% with carbon dioxide laser<br>5% with variable pulse erbium:YAG laser<br>Within-participant comparison (opposite sides of the face)<br>Some hypopigmentation was still visible at 6 months<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of dermatologists also assessed outcomes | P <0.05 | ○○○ | variable pulse erbium:YAG laser |
| [28]<br>RCT | 19 women and 2 men, aged 18–90 years, with perioral or periorbital wrinkles, Fitzpatrick skin types I–III<br>In review [13] | **Hyperpigmentation**<br>29% with carbon dioxide laser<br>24% with variable pulse erbium:YAG laser<br>Within-participant comparison (opposite sides of the face)<br>Hyperpigmentation resolved spontaneously in all cases within 6 months<br>Investigators and participants were not blinded to treatment allocation, but a blinded panel of dermatologists also assessed outcomes | | | |
| [29]<br>RCT | 28 people with mild to moderate periorbital rhytides ('crow's feet') at rest (Fitzpatrick skin type II – fine to moderate depth wrinkles, moderate number of lines) | **Adverse effects**<br>with fractional carbon dioxide laser<br>with fractional erbium:YAG laser<br>Within-participant comparison (opposite sides of the face)<br>See Further information on studies for enhanced reporting of adverse effects from this study | The RCT reported various significant differences between groups, which varied by time (i.e., short term to longer term); see Further information on studies | | |

No data from the following reference on this outcome. [13]

### Carbon dioxide laser versus carbon dioxide laser plus variable pulse erbium:YAG laser:

We found one systematic review (search date 2002) [13] comparing carbon dioxide laser versus carbon dioxide laser plus variable pulse erbium:YAG laser, which identified one RCT involving 20 women.

#### Wrinkle improvement

*Carbon dioxide laser compared with carbon dioxide laser plus variable pulse erbium:YAG laser* We don't know how carbon dioxide laser and carbon dioxide laser plus variable pulse erbium:YAG laser compare at improving wrinkles (very low-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in wrinkles** | | | | | |
| [13] Systematic review | 20 women, aged 42–72 years, with Fitzpatrick skin types I–III on the upper lip<br>Data from 1 RCT | **Wrinkle improvement , 4 months**<br>67% with carbon dioxide laser alone<br>68% with carbon dioxide laser plus variable pulse erbium:YAG laser | Reported as not significant<br>P value not reported | ⟷ | Not significant |

### Quality of life

No data from the following reference on this outcome. [13]

### Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [13] Systematic review | 20 women, aged 42–72 years, with Fitzpatrick skin types I–III on the upper lip<br>Data from 1 RCT | **Erythema**<br>with carbon dioxide laser alone<br>with carbon dioxide laser plus variable pulse erbium:YAG laser | Reported as not significant<br>P value not reported | ⟷ | Not significant |
| [13] Systematic review | 20 women, aged 42–72 years, with Fitzpatrick skin types I–III on the upper lip<br>Data from 1 RCT | **Pain**<br>with carbon dioxide laser alone<br>with carbon dioxide laser plus variable pulse erbium:YAG laser | Reported as not significant<br>P value not reported | ⟷ | Not significant |

### Further information on studies

[13] Carbon dioxide laser versus dermabrasion: two of the RCTs included in the review reported withdrawal rates of 1/20 (5%) [23] and 1/15 (7%). [30] The third RCT gave no information on withdrawal rates.

[13] [23] Carbon dioxide laser versus dermabrasion: in the RCT [23] identified by the review, [13] 85% of women (20 women in RCT) had erythema on the upper lip (similar for both groups) 1 month after treatment. In 10% of people, erythema was reported to be worse on the laser-treated side, and in 5%, on the dermabrasion-treated side. The average duration of erythema was 2.5 months for both treatments. Pain, oedema, eczema, and whiteheads resolved either spontaneously or with minimal treatment.

[29] Adverse effects: Carbon dioxide laser versus erbium:YAG laser: the RCT found significantly more pain (P <0.001), burning/itching (P <0.01), and secretion (P <0.01) in the erbium:YAG laser group compared with the carbon dioxide laser group at 1 day, but significantly more bleeding (P <0.0001) in the carbon dioxide laser group. At 3 days, there was still significantly more burning/itching (P <0.05) and secretion (P <0.05) in the erbium:YAG laser group. At 6 days, there was significantly more erythema (P <0.01) and swelling (P <0.05) in the carbon dioxide laser group compared with the erbium:YAG laser group. At 6 months, there was significantly more hyperpigmentation (P <0.01) with carbon dioxide laser. All adverse effects were rated on site by a 'physician assistant' using a 10-point visual analogue scale (further details of the clinical importance of effects not supplied). **General:** the RCT was independent of funding by a manufacturer. The RCT only used a single treatment session.

**Comment:** The effects of chemical peels and carbon dioxide lasers are likely to be dependent on the technique of the dermatological surgeon; therefore, results may not generalise to different populations. [13] The available evidence is too weak to define the effects of carbon dioxide laser on wrinkles.

## OPTION DERMABRASION

- For GRADE evaluation of interventions for Wrinkles, see table, p 46 .
- We found no direct information about whether dermabrasion is better than placebo.
- We don't know whether dermabrasion is more effective at improving wrinkles compared with carbon dioxide laser treatment, as studies have given inconclusive results, but adverse effects are common with both treatments, especially erythema.

### Benefits and harms

**Dermabrasion versus placebo:**

We found no systematic reviews or RCTs.

**Dermabrasion versus carbon dioxide laser:**

See option on Carbon dioxide laser, p 23 .

**Comment:** None.

## OPTION VARIABLE PULSE ERBIUM:YAG LASER

- For GRADE evaluation of interventions for Wrinkles, see table, p 46 .
- We found no direct information from RCTs about whether erbium:YAG laser is better than placebo.
- We don't know whether erbium:YAG laser is more effective than carbon dioxide laser at improving wrinkles, as studies have given inconclusive results.

### Benefits and harms

**Variable pulse erbium:YAG laser versus placebo:**

We found no systematic review or RCTs.

**Variable pulse erbium:YAG laser versus carbon dioxide laser:**

See option on Carbon dioxide laser, p 23 .

**Variable pulse erbium:YAG laser plus carbon dioxide laser versus carbon dioxide laser:**

See option on Carbon dioxide laser, p 23 .

**Comment:** **Variable pulse erbium:YAG laser versus carbon dioxide laser:**
See comment on Carbon dioxide laser, p 23 .

## OPTION BOTULINUM TOXIN INJECTION (E.G., BOTULINUM TOXIN TYPE A AND TYPE B) New

- For GRADE evaluation of interventions for Wrinkles, see table, p 46 .
- Botulinum toxin injection (given in a single session) seems to be more effective than placebo at improving wrinkles at up to 120 days.
- We found no RCTs comparing repeated injections of botulinum toxin versus placebo over a long period of time.

## Benefits and harms

### Botulinum toxin injection versus placebo:

We found 19 RCTs. [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] [49] The RCTs reported multiple outcome measures over different time periods. We reported the primary outcome measure that used a recognised scale, where possible. We mainly reported one outcome per trial, which was often at 30 days follow-up. As many of the RCTs used different outcome measures, we have reported in detail each measure that was used. A number of the RCTs were dose-finding trials. In these trials, we were only interested in the effects of botulinum toxin injection versus placebo; therefore, not all treatment (dosing) arms have been reported (see Further information on studies).

#### Wrinkle improvement

*Botulinum toxin injection versus placebo* Botulinum toxin injection (given in a single session) seems to be more effective than placebo at improving glabellar line severity, crow's feet, and wrinkle scores at up to 120 days, but we found no evidence in the longer term and when repeated injections are used (moderate-quality evidence).

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Improvement in wrinkles** | | | | | |
| [31]<br>RCT | 276 people, aged 18 years or over, with moderate to severe glabellar frown lines at maximum frown (score of 2 or 3 on the Facial Wrinkle Scale)<br>Multi-centre trial | **Proportion of people achieving treatment success (at least 2 point improvement at maximal frown on the 4-point Facial Wrinkle Scale assessed by investigator, and at least 2 point improvement from baseline assessed by participant using a 4-point scale [0 = no muscle action to 3 = strong muscle action possible that may cause local pallor]) , at day 30**<br>111/184 (60%) with incobotulinumtoxinA (5 injection sites used in 1 session)<br>0/92 (0%) with placebo | P <0.001<br>Randomised 2:1 to treatment group | ○○○ | botulinum toxin injection |
| [32]<br>RCT | 271 people, aged 18 years or over, with moderate to severe glabellar frown lines at maximum frown (score of 2 or 3 on the Facial Wrinkle Scale)<br>Multi-centre trial | **Proportion of people achieving treatment success (at least 2 point improvement at maximal frown on the 4-point Facial Wrinkle Scale assessed by investigator and at least 2 point improvement from baseline assessed by participant using a 4-point scale [0 = no muscle action to 3 = strong muscle action possible that may cause local pallor] , at day 30**<br>87/182 (48%) with incobotulinumtoxinA (5 injection sites used in 1 session)<br>0/89 (0%) with placebo | P <0.001<br>Randomised 2:1 to treatment group | ○○○ | botulinum toxin injection |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [33]<br>RCT | 227 people, aged 18 to 65 years, with moderate to severe glabellar lines at maximum frown (score of 2 or above on the Facial Wrinkle Scale)<br>4 centres in China | **Proportion of responders (participants who achieved investigator's rating of none or mild severity on Facial Wrinkle Scale at maximum frown) , at day 30**<br>160/170 (94%) with botulinum toxin type A (BoNT-A; 5 injection sites used in 1 session)<br>2/57 (4%) with placebo | P <0.001<br>Randomised 3:1 to treatment group | ○○○ | botulinum toxin injection |
| [34]<br>RCT<br>**4-armed trial** | 162 people, aged 18 to 65 years, with moderate to severe (grade 2 or 3) crow's feet during maximum smile, and mild to severe (grade 1, 2, or 3) crow's feet at rest on both sides of the face | **Response at maximum smile (defined as an improvement in severity of crow's feet from moderate or severe [grade 2 or 3] at baseline to none or mild [grade 0 or 1] on both sides) assessed by panel review of standardised photographs , at week 4**<br>with botulinum toxin type A (BoNT-A)<br>with placebo<br>Absolute results not reported<br>BoNT-A given in 3 arms with different doses | P <0.001 for each dose versus placebo | ○○○ | botulinum toxin injection |
| [35]<br>RCT | 158 people, aged 18 years and over, with moderate to severe glabellar lines according to investigator and self-assessment using a 4-point scale<br>3 centres | **Proportion of responders (from 3 [severe] or 2 [moderate] at baseline to 1 [mild] or 0 [none]; investigator assessment at maximum frown) , at day 30**<br>92/103 (89%) with botulinum toxin type A (BoNT-A)<br>2/51 (4%) with placebo | P <0.001<br>Randomised 2:1 to treatment group | ○○○ | botulinum toxin injection |
| [35]<br>RCT | 158 people, aged 18 years and over, with moderate to severe glabellar lines according to investigator and self-assessment using a 4-point scale<br>3 centres | **Proportion of responders (from 3 [severe] or 2 [moderate] at baseline to 1 [mild] or 0 [none]; participant assessment at maximum frown) , at day 30**<br>78/103 (76%) with botulinum toxin type A (BoNT-A)<br>5/51 (10%) with placebo | P <0.001<br>Randomised 2:1 to treatment group | ○○○ | botulinum toxin injection |
| [36]<br>RCT | 142 people with moderate to severe glabellar lines (GLSS rating of 2 or 3 on a 4-point scale)<br>6 study sites | **Proportion of responders (defined as Glabellar Line Severity Scale [GLSS] 2 or 3 at baseline and 0 or 1 assessed by investigator and participant) , at day 30**<br>76% with botulinum toxin type A (BoNT-A; 5 injection sites used in 1 session)<br>0% with placebo<br>Absolute numbers not reported<br>Participants previously had 1 or 2 open-label treatments and 1 randomised treatment, and were further randomised after this | P <0.001<br>Highly selected population | ○○○ | botulinum toxin injection |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [37]<br>RCT<br>**3-armed trial** | 142 Japanese people, aged 20 to 64 years, with glabellar lines of at least moderate severity at maximal contraction (score of 2 or more on a 4-point scale) | **Proportion of responders (defined as those with post-treatment scores of 0 or 1 on physician-rated line severity at maximal contraction [frown]) , at week 4**<br>with botulinum toxin type A (BoNT-A)<br>with placebo<br>Absolute results not reported<br>BoNT-A given in 2 arms with different doses | P <0.001 for each dose versus placebo | ○○○ | botulinum toxin injection |
| [38]<br>RCT<br>**8-armed trial** | 139 people, aged 25 to 60 years, with mild or moderate glabellar lines at rest or severe glabellar lines at full frown (measured on a 4-point scale where<br>0 = none and<br>3 = severe)<br>3 centres | **Mean change from baseline in Investigator Global Scale at rest , at week 4**<br>with botulinum toxin type B (BTX-B)<br>with placebo<br>Absolute results not reported<br>(BTX-B) given in 7 arms with different doses | All doses were significantly better than placebo except the 2 lowest doses<br>P values not reported | ○○○ | botulinum toxin injection |
| [39]<br>RCT | 40 women, aged 18 to 65 years, with moderate or severe glabellar lines, forehead lines, and crow's feet (measured on a 4-point scale where 0 = none and 3 = severe) | **Facial Wrinkle Scale score of 0 (none) or 1 (mild) at rest , at week 4**<br>with botulinum toxin type A (BoNT-A)<br>with placebo<br>Absolute results not reported | Significant improvement *v* placebo in glabella (P = 0.0003), crow's feet (P = 0.003), and forehead (P <0.0001) scores | ○○○ | botulinum toxin injection |
| [40]<br>RCT | 70 women, aged 30 to 55 years, with moderate or severe glabellar lines at maximum contraction (measured on a 4-point scale where<br>0 = none to 3 = severe) | **Mean change from baseline in investigator assessment of glabellar line severity at rest (severity assessed on the 4-point Facial Wrinkle Scale [0 = none to 3 = severe] , at week 4**<br>1.7 to 0.5 with botulinum toxin type A (BOTOX; 5 injection sites used in 1 session)<br>1.7 to 1.7 with placebo | P = 0.001 | ○○○ | botulinum toxin injection |
| [41]<br>RCT<br>**4-armed trial** | 373 people with moderate or severe vertical glabellar lines at maximum frown | **Proportion of responders (defined as having a rating of 0 [none] or 1 [mild] on investigator's assessment of glabellar lines at maximum frown) , up to day 120**<br>with botulinum toxin type A (Reloxin; 5 injection sites used in 1 session)<br>with placebo<br>Absolute results not reported<br>Botulinum toxin type A (Reloxin) given in 3 arms with different doses | P <0.001 for all treatment arms versus placebo | ○○○ | botulinum toxin injection |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [42]<br>RCT | 109 people with moderate or severe vertical or diagonal glabellar wrinkles at maximum frown (score of 2 or 3 on a standardised 4-point clinical scale ranging from 0 = none to 3 = severe); and mild, moderate, or severe vertical or diagonal glabellar wrinkles at rest (score of 1, 2, or 3) | **Proportion of responders (defined as a reduction of at least 1 point on wrinkle severity graded by 4 experts using photographs and a standardised clinical scale [0 = none to 3 = severe] at maximal frown) , from weeks 0 to 4**<br>62/72 (86%) with botulinum toxin type A (Dysport; 3 injection sites used in 1 session)<br>7/37 (19%) with placebo<br>RCT split between study centres, which used either 3 or 5 injection sites per session (see reporting below) | P <0.001<br>Randomised 2:1 to treatment group | ○○○ | botulinum toxin injection |
| [42]<br>RCT | 111 people with moderate or severe vertical or diagonal glabellar wrinkles at maximum frown (score of 2 or 3 on a standardised 4-point clinical scale ranging from 0 = none to 3 = severe); and mild, moderate, or severe vertical or diagonal glabellar wrinkles at rest (score of 1, 2, or 3) | **Proportion of responders (defined as a reduction of at least 1 point on wrinkle severity graded by 4 experts using photographs and a standardised clinical scale [0 = none to 3 = severe] at maximal frown) , from weeks 0 to 4**<br>63/73 (86%) with botulinum toxin type A (Dysport; 5 injection sites used in 1 session)<br>3/38 (8%) with placebo<br>RCT split between study centres, which used either 3 or 5 injection sites per session (see reporting above) | P <0.001<br>Randomised 2:1 to treatment group | ○○○ | botulinum toxin injection |
| [43]<br>RCT<br>**5-armed trial** | 77 women, aged 18 to 65 years, with clinically diagnosed moderate-to-severe glabellar lines at maximum frown (score of 2 or 3 on the Facial Wrinkle Scale) | **Mean severity of frown lines at maximum frown (physician evaluated) , at weeks 4, 8 and 12**<br>with botulinum toxin type A (5 injection sites used in 1 session)<br>with placebo<br>Absolute results not reported<br>Remaining 3 arms assessed over-the-counter topical cosmetic products | P <0.001<br>Reported as significantly lower for botulinum toxin injection versus placebo at each time point | ○○○ | botulinum toxin injection |
| [44]<br>RCT | 20 women with mentalis rhytids (chin wrinkles) of at least moderate severity (score of 2 or above on the Facial Wrinkle Scale) | **Mean change from baseline in patient-evaluated Facial Wrinkle Scale at repose , at week 4**<br>–1.32 with botulinum toxin type A<br>–0.21 with placebo<br>Absolute results reported graphically<br>Split-face trial: botulinum toxin type A applied to one side of chin, placebo applied to other side of chin<br>People acted as their own controls (half of face received each treatment) | P = 0.0056 | ○○○ | botulinum toxin injection |
| [45]<br>RCT | 162 people, aged 18 to 65 years, with bilaterally | **Proportion of responders (defined as investigator assessed improvement of at least 1** | P <0.05 for all treatment arms versus placebo | ○○○ | botulinum toxin injection |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **5-armed trial** | symmetrical moderate or severe crow's feet at maximal smile (measured on a 4-point scale)<br>10 centres | **grade at maximal smile) , at day 30**<br>with botulinum toxin type A (BTX-A; single bilateral treatment)<br>with placebo<br>Absolute results not reported<br>Botulinum toxin type A (BTX-A) given to 4 arms with different doses | | | |
| [46]<br>RCT<br>**4-armed trial** | 119 people with moderate to severe glabellar lines at maximal frown and at rest (score of 2 or more on a 4-point scale)<br>3 centres | **Proportion of responders (defined as grade 0 or 1 glabellar line at rest from independent assessors rating photographs) , at 1 month after treatment**<br>with botulinum toxin type A (BTX-A; Dysport)<br>with placebo<br>Absolute results not reported<br>Botulinum toxin type A (BTX-A; Dysport) given in 3 arms with different doses | P values ranged from P = 0.015 to P = 0.005<br>All treatment arms were significantly better versus placebo | ○○○ | botulinum toxin injection |
| [47]<br>RCT | 273 people with glabellar lines of at least moderate severity at maximal frown (score of 2 or above on a 4-point scale) | **Proportion of responders (physician's rating of none or mild severity at maximal frown) , at day 120**<br>49/201 (24%) with botulinum toxin type A (5 injection sites used in 1 session)<br>2/68 (3%) with placebo | P <0.001<br>Randomised 3:1 to treatment group<br>Longest timeframe reported. Also significant difference between groups at days 7, 30, 60, and 90 | ○○○ | botulinum toxin injection |
| [48]<br>RCT | 264 people, aged 18 to 75 years, with glabellar lines of at least moderate severity at maximal frown (score of 2 or above on a 4-point scale)<br>16 centres | **Physician's assessment of glabellar lines severity at maximum frown on a 4-point scale (0 = none to 3 = severe) , at day 120**<br>1.99 with botulinum toxin type A (BTX-A; 5 injection sites used in 1 session)<br>2.58 with placebo | P <0.001<br>Randomised in 3:1 ratio<br>Longest timeframe reported; also significant difference between groups at days 7, 30, 60, and 90 | ○○○ | botulinum toxin injection |
| [49]<br>RCT<br>**4-armed trial** | 60 adults with bilateral symmetrical moderate to severe crow's feet with maximum muscle contraction | **Proportion of responders (at least 1 point improvement on the Facial Wrinkle Scale) at maximum contraction as assessed by a trained observer , at week 4**<br>with botulinum toxin type A (BTX-A; BOTOX; 3 injection sites used in 1 session, to 1 side of the face)<br>with placebo<br>Absolute results reported graphically<br>Botulinum toxin type A given in 3 arms with different doses<br>Split-face trial: botulinum toxin type A (BTX-A; BOTOX) given to one side of the face, placebo given to other side of the face<br>People acted as their own control (half of face received each treatment) | P <0.029<br>All treatment arms were significantly better versus placebo | ○○○ | botulinum toxin injection |

## Quality of life

No data from the following reference on this outcome. [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] [49]

## Adverse effects

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| **Adverse effects** | | | | | |
| [31]<br>RCT | 276 people, aged 18 years or over, with moderate to severe glabellar frown lines at maximum frown (score of 2 or 3 on the Facial Wrinkle Scale)<br>Multi-centre trial | **Adverse effects**<br>13/184 (7%) with incobotulinumtoxin A<br>2/92 (2%) with placebo<br>Headache was the most common effect, noted in 7 people with incobotulinumtoxin A, and 2 people with placebo<br>Two people with incobotulinumtoxin A had facial paresis, described as mild and resolved | Significance not reported | | |
| [32]<br>RCT | 271 people, aged 18 years or over, with moderate to severe glabellar frown lines at maximum frown (score of 2 or 3 on the Facial Wrinkle Scale)<br>Multi-centre trial | **Adverse effects**<br>22/182 (12%) with incobotulinumtoxin A<br>2/89 (2%) with placebo<br>Headache was the most common effect, noted in 7% people with incobotulinumtoxin A<br>Two people (1%) with incobotulinumtoxin A had headache, sinusitis, and ear infection | Significance not reported | | |
| [33]<br>RCT | 227 people, aged 18 to 65 years, with moderate to severe glabellar lines at maximum frown (score of 2 or above on the Facial Wrinkle Scale)<br>4 centres in China | **Adverse effects**<br>with botulinum toxin type A (BoNT-A)<br>with placebo<br>The most frequently reported treatment-related adverse effects were headache (15/170 [9%] with BoNT-A *v* 1/57 [2%] with placebo, P = 0.8), and abnormal sensation in the eye (9/170 [5%] with BoNT-A *v* 0/57 [0%] with placebo, P = 0.12)<br>One person in the BoNT-A group reported ptosis | Significance of overall analysis for treatment-related adverse effects not reported | | |
| [34]<br>RCT<br>**4-armed trial** | 162 people, aged 18 to 65 years, with moderate to severe (grade 2 or 3) crow's feet during maximum smile, and mild to severe (grade 1, 2, or 3) crow's feet at rest on both sides of the face | **Adverse effects**<br>with botulinum toxin type A (BoNT-A)<br>with placebo<br>Absolute results not reported<br>4-armed dose-finding trial<br>Most frequent treatment-related adverse effect was mild periorbital haematoma (10% of all subjects; further details not reported) | Analysis versus placebo not reported | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | | One person in the highest-dose group reported eyelid ptosis, which had resolved on day 31 after treatment | | | |
| [35]<br>RCT | 158 people, aged 18 years and over, with moderate to severe glabellar lines according to investigator and self-assessment using a 4-point scale<br>3 centres | **Adverse effects probably or possibly related to treatment**<br>23% with botulinum toxin type A (BoNT-A)<br>15% with placebo<br>Absolute numbers not reported<br>Adverse effects were primarily injection site problems and problems around the eyes<br>Three people had ptosis with active treatment, all starting within 17 days and resolving between 39 and 85 days | P value not reported | | |
| [36]<br>RCT | 142 people with moderate to severe glabellar lines (GLSS rating of 2 or 3 on a 4-point scale)<br>6 study sites | **Treatment-emergent adverse events**<br>38% with botulinum toxin type A (BoNT-A)<br>30% with placebo<br>Absolute numbers not reported<br>Participants previously had 1 or 2 open-label treatments and 1 randomised treatment, and were further randomised after this | Significance not reported | | |
| [37]<br>RCT<br>**3-armed trial** | 142 Japanese people, aged 20 to 64 years, with glabellar lines of at least moderate severity at maximal contraction (score of 2 or more on a 4-point scale) | **Adverse effects**<br>with botulinum toxin type A (BoNT-A)<br>with placebo<br>Absolute results not reported<br>Two people developed blepharoptosis (1 in each treatment group) and 12 people experienced heavy eyelids (11 in the treatment groups, and 1 with placebo) | Reported as not significantly different between groups | | |
| [38]<br>RCT | 139 people, aged 25 to 60 years, with mild or moderate glabellar lines at rest or severe glabellar lines at full frown (measured on a 4-point scale where 0 = none and 3 = severe)<br>3 centres | **Adverse effects**<br>38% with botulinum toxin type B (BTX-B)<br>33% with placebo<br>Absolute numbers not reported<br>The most common treatment-related adverse effect was headache (18/139 people [13%]) | Significance not reported | | |
| [39]<br>RCT | 40 women, aged 18 to 65 years, with moderate or severe glabellar lines, forehead lines, and crow's feet (measured on a 4-point scale where 0 = none to 3 = severe) | **Adverse effects**<br>with botulinum toxin type A (BoNT-A)<br>with placebo<br>Absolute results not reported<br>Two people in the treatment group experienced a tight feeling across the forehead and pulling lines on upper outer eyelids | | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| [40]<br>RCT | 70 women, aged 30 to 55 years, with moderate or severe glabellar lines at maximum contraction (measured on a 4-point scale where 0 = none to 3 = severe) | **Adverse effects**<br>with botulinum toxin type A (BOTOX)<br>with placebo<br>1 person had mild bruising at an injection site | | | |
| [41]<br>RCT<br>**4-armed trial** | 373 people with moderate or severe vertical glabellar lines at maximum frown | **Adverse effects**<br>with botulinum toxin type A (Reloxin)<br>with placebo<br>Mild ptosis was reported in 3 people on day 7 with active treatment | | | |
| [42]<br>RCT | 109 people with moderate or severe vertical or diagonal glabellar wrinkles at maximum frown (score of 2 or 3 on a standardised 4-point clinical scale ranging from 0 = none to 3 = severe); and mild, moderate, or severe vertical or diagonal glabellar wrinkles at rest (score of 1, 2, or 3) | **Adverse effects (causal relationship could not be excluded)**<br>with botulinum toxin A (Dysport; 3 injection sites used in 1 session)<br>with placebo<br>3 people treated with 3 injections of botulinum had hypaesthesia, discomfort at injection site, heavy eyelids, and 'Spock' eyebrow; 2 people receiving placebo (3 injections) had headache and pyrexia | | | |
| [42]<br>RCT | 111 people with moderate or severe vertical or diagonal glabellar wrinkles at maximum frown (score of 2 or 3 on a standardised 4-point clinical scale ranging from 0 = none to 3 = severe); and mild, moderate, or severe vertical or diagonal glabellar wrinkles at rest (score of 1, 2, or 3) | **Adverse effects (causal relationship could not be excluded)**<br>with botulinum toxin A (Dysport, 5 injection sites used in 1 session)<br>with placebo<br>8 people treated with 5 injections of botulinum toxin had adverse effects (4 had headache, 4 others had 'Spock' eyebrow, hoarseness, dizziness, and eyelid ptosis); 4 people receiving placebo (5 injections) had headache, dizziness, blepharochalasis, and swollen face | | | |
| [43]<br>RCT<br>**5-armed trial** | 77 women, aged 18 to 65 years, with clinically diagnosed moderate-to-severe glabellar lines at maximum frown (score of 2 or 3 on the Facial Wrinkle Scale) | **Adverse effects**<br>with botulinum toxin type A<br>with placebo<br>Remaining 3 arms assessed over-the-counter topical cosmetic products<br>No adverse effects reported | | | |
| [44]<br>RCT | 20 women with mentalis rhytids (chin wrinkles) of at least moderate severity (score of 2 or above on the | **Adverse effects**<br>with botulinum toxin type A<br>with placebo<br>Split-face trial: people acted as their own controls (half of face received each treatment) | | | |

| Ref (type) | Population | Outcome, Interventions | Results and statistical analysis | Effect size | Favours |
|---|---|---|---|---|---|
| | Facial Wrinkle Scale) | No adverse effects reported | | | |
| [45]<br>RCT<br>**5-armed trial** | 162 people, aged 18 to 65 years, with bilaterally symmetrical moderate or severe crow's feet at maximal smile (measured on a 4-point scale)<br>10 centres | **Adverse effects**<br>with botulinum toxin type A (BTX-A)<br>with placebo<br>Absolute results not reported<br>Most frequent treatment-related adverse effects were injection site bruising (8% overall) and headache (5% overall); further details not reported | Reported as no statistically significant differences among treatment groups | | |
| [46]<br>RCT<br>**4-armed trial** | 119 people with moderate to severe glabellar lines at maximal frown and at rest (score of 2 or more on a 4-point scale)<br>3 centres | **Adverse effects possibly or probably related to treatment**<br>with botulinum toxin type A (BTX-A)<br>with placebo<br>In the treatment group: 2 cases of headache, 1 case of migraine, forehead rigidity, vertigo, rosacea, forehead muscle spasm, and forehead ecchymosis<br>One forehead ecchymosis reported in the placebo group | | | |
| [47]<br>RCT | 273 people with glabellar lines of at least moderate severity at maximal frown (score of 2 or above on a 4-point scale) | **Adverse effects**<br>with botulinum toxin type A<br>with placebo | Reported that individual adverse events were at similar rates for the two groups (P >0.5) | | |
| [48]<br>RCT | 264 people, aged 18 to 75 years, with glabellar lines of at least moderate severity at maximal frown (score of 2 or above on a 4-point scale)<br>16 centres | **Adverse effects**<br>with botulinum toxin type A (BTX-A)<br>with placebo<br>In the BTX-A group, blepharoptosis was reported for 11/203 (5%) people and 12/406 (3%) of eyes (almost all ptosis unilateral)<br>8 cases were moderate and resolved in an average of 20 days; 4 cases were moderate and resolved in an average of 40 days | Reported that there were no statistical differences in adverse effects between groups | | |
| [49]<br>RCT<br>**4-armed trial** | 60 adults with bilateral symmetrical moderate to severe crow's feet with maximum muscle contraction | **Adverse effects**<br>with botulinum toxin type A (BTX-A)<br>with placebo<br>Most common adverse effect was mild bruising, seen in 11% to 25% of people in the different groups | | | |

**Further information on studies**

[31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] [49]

The RCTs reported the use of a variety of preparations, outcomes, and timeframes. They found a consistent improvement with botulinum toxin injection compared with placebo over these varying analyses. Many of the RCTs were described as being double-blinded. However, almost all studies were funded by pharmaceutical companies, and in some cases the sponsor was involved in the design, writing, and final approval of the manuscript.

**Comment:** Many of the RCTs examined the effects of botulinum toxin injection up to 120 days, and some reported outcomes up to 180 days. [34] [45] [46] We found no RCT that reported longer-term outcomes. They all assessed the effects of a single treatment episode. One RCT assessed the effects of injection after a previous open-label treatment period and previous participation in an RCT. [36] We found no RCTs that examined the effects of multiple repeat injection episodes of botulinum toxin versus placebo over a longer period of time.

## GLOSSARY

**Botulinum toxin** A neurotoxin produced by the bacterium Clostridium botulinum. There are eight antigenically distinguishable subtypes (A, B, C1, C2, D, E, F and G). Type A is the most potent toxin, followed by types B and F. Botulinum toxin works by blocking the release of acetylcholine – the principal neurotransmitter at the neuromuscular junction, thus interfering with neural transmission. Subtypes A and B are the only commercially available form of botulinum toxin for clinical use.

**Fitzpatrick skin phototype classification** I = always burns easily, never tans; II = always burns easily, tans minimally; III = burns moderately, tans gradually (light brown); IV = burns minimally, always tans well (brown); V = rarely burns, tans profusely (dark brown); VI = never burns, deeply pigmented (black).

**Mild/moderate/severe photodamage** A spectrum of features including wrinkles, hyperpigmentation, tactile roughness, and telangiectasia. Usually measured on a scale from 0–9 (0 = none, 1–3 = mild, 4–6 = moderate, and 7–9 = severe).

**Erbium:YAG laser** An yttrium aluminium garnet laser. Laser delivered in short pulse durations with relatively long intervening time periods between each pulse is referred to as ‘variable pulsed’. Laser delivered via a laser beam divided into thousands of microscopic treatment zones that target a fraction of the skin is referred to as ‘fractional’.

**Low-quality evidence** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Moderate-quality evidence** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Very low-quality evidence** Any estimate of effect is very uncertain.

**Visual Analogue Scale (VAS)** A commonly used scale in pain assessment. It is a 10-cm horizontal or vertical line with word anchors at each end, such as 'no pain' and 'pain as bad as it could be'. The person is asked to make a mark on the line to represent pain intensity. This mark is converted to distance in either centimetres or millimetres from the 'no pain' anchor to give a pain score that can range from 0–10 cm or 0–100 mm.

## SUBSTANTIVE CHANGES

**Botulinum toxin injection (e.g. botulinum toxin type A and type B)** New option. Evidence added. [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] [49] Categorised as beneficial.

**Carbon dioxide laser** New evidence added. [29] Categorisation unchanged (unknown effectiveness).

**Variable pulse erbium:YAG laser** New evidence added. [29] Categorisation unchanged (unknown effectiveness).

**Chemical peel (including alpha and beta hydroxyl acids)** Previous option re-structured to now include alpha and beta hydroxyl acids (e.g., glycolic and lactic acids). Categorisation unchanged (unknown effectiveness).

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Competing interests: JJM, KC, CVK, and IHF declare that they have no competing interests.

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**GRADE** **Evaluation of interventions for Wrinkles.**

| Important outcomes | | | Adverse effects, Quality of life, Wrinkle improvement | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Studies (Participants) | Outcome | Comparison | Type of evidence | Quality | Consistency | Directness | Effect size | GRADE | Comment |
| *What are the effects of treatments for skin wrinkles?* | | | | | | | | | |
| 2 (912) [14] [15] | Wrinkle improvement | Tazarotene versus placebo/vehicle cream | 4 | –1 | –1 | 0 | 0 | Low | Quality point deducted for incomplete reporting of results; consistency point deducted for inconsistent effect with different doses |
| 2 (291) [13] [16] | Wrinkle improvement | Tazarotene versus tretinoin | 4 | –2 | –1 | 0 | 0 | Very low | Quality points deducted for uncertainty about randomisation and allocation concealment, and inconsistent assessment of results; consistency point deducted for conflicting results |
| 13 (1480) [13] [17] | Wrinkle improvement | Tretinoin versus vehicle cream | 4 | –3 | 0 | 0 | 0 | Very low | Quality points deducted for uncertainty about randomisation and allocation concealment, inconsistent assessment of results, and short-term follow-up in some RCTs; consistency point deducted for conflicting results, but added for dose response |
| 2 (1099) [13] [21] | Wrinkle improvement | Isotretinoin versus vehicle cream | 4 | –3 | 0 | 0 | 0 | Very low | Quality points deducted for poor follow-up, no intention-to-treat analysis, and incomplete reporting of results |
| 2 (149) [13] | Wrinkle improvement | Glycolic acid versus vehicle cream | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data, and incomplete reporting of results; directness point deducted for uncertainty about clinical significance of the outcome; consistency point deducted for conflicting results, but added for possible dose response |
| 1 (74) [13] | Wrinkle improvement | Lactic acid versus vehicle cream | 4 | –2 | 0 | –1 | 0 | Very low | Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for uncertainty about clinical significance of the outcome |
| 3 (55) [13] | Wrinkle improvement | Carbon dioxide laser versus dermabrasion | 4 | –2 | 0 | 0 | 0 | Low | Quality points deducted for sparse data and incomplete reporting of results |
| 2 (44) [13] [25] | Wrinkle improvement | Carbon dioxide laser versus chemical peel (including alpha and beta hydroxyl acids) | 4 | –3 | –1 | 0 | 0 | Very low | Quality points deducted for sparse data, inadequate blinding, and incomplete reporting of results; consistency point deducted for contradictory results |
| 4 (83) [26] [27] [28] [29] | Wrinkle improvement | Carbon dioxide laser versus erbium:YAG laser | 4 | –3 | –1 | –1 | 0 | Very low | Quality points deducted for sparse data, incomplete blinding, and incomplete reporting of results; consistency point deducted for conflicting results; directness point deducted for different outcomes assessed |

| Important outcomes | | | Adverse effects, Quality of life, Wrinkle improvement | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Studies (Participants)** | **Outcome** | **Comparison** | **Type of evidence** | **Quality** | **Consistency** | **Directness** | **Effect size** | **GRADE** | **Comment** |
| 1 (20) [13] | Wrinkle improvement | Carbon dioxide laser versus carbon dioxide laser plus variable pulse erbium:YAG laser | 4 | –3 | 0 | 0 | 0 | Very low | Quality point deducted for sparse data, incomplete blinding, and incomplete reporting of results |
| 19 (3195) [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43] [44] [45] [46] [47] [48] [49] | Wrinkle improvement | Botulinum toxin injection versus placebo | 4 | –1 | 0 | 0 | 0 | Moderate | Quality point deducted for weak methods (possible bias, and pharmaceutical involvement in publications) |

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.