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A guide to actinic keratosis treatments

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Topical therapy				
Treatment	**Category**	**Mechanism of action**	**Effectiveness**	**Common adverse effects/limitations**
5-fluorouracil (5-FU) topical monotherapy	Field-directed, FDA-approved	Thymidylate synthase inhibition, blocks DNA synthesis.	Among the most effective field therapies; high clearance rates	Dihydropyrimidine dehydrogenase deficiency can lead to myelosuppression, severe mucositis, and neurological issues.
Imiquimod (3.75% or 5%)	Field-directed, FDA-approved	TLR-7 activation, induces interferon and cellular immunity	High efficacy	Erythema, blistering, necrosis, burning, flu-like symptoms (especially with larger treated areas), and psoriasis exacerbation.
Diclofenac 3% gel (Solaraze)	Field-directed, FDA-approved	COX-2 inhibition reduces proliferation and angiogenesis.	Mild to moderate efficacy	Mild irritation. Do not use in people with hypersensitivity to NSAIDs or bleeding disorders. Classified as pregnancy category B.
Tirbanibulin (Klisyri)	Field-directed, FDA-approved	Src kinase inhibition and microtubule disruption	Moderate to high efficacy	Skin reaction with pruritus and pain.
Ingenol mebutate (historical, withdrawn)	No longer available in the United States	Causes rapid cell death, with antibody-dependent neutrophil cytotoxicity; then provokes a robust inflammatory phase through PKC activation.	Limited efficacy	Local irritation (erythema, scaling, crusting) most pronounced on days 4-7; risk of skin cancer.
5-FU plus calcipotriene combination therapy (off label)	Field-directed combination, not FDA-approved	Acts synergistically by inducing TSLP-mediated $CD4^+$ T-cell immunity.	Studies have shown greater efficacy and greater clearance, often >60% after only 4 days; may reduce future SCC risk	Intense localized inflammation, burning, and crusting.
Chemical peels (e.g., TCA, Jessner's Solution + TCA)	Field-directed, older	Controlled chemical destruction of epidermis	Moderate to lower efficacy compared to conventional PDT and 5FU	Risk of infections, dyspigmentation, scarring, and delayed healing.

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Photodynamic therapy				
Treatment	**Category**	**Mechanism of action**	**Effectiveness**	**Common adverse effects/limitations**
ALA 20% plus BLU-U blue light PDT*	Field-directed, FDA-approved	Topical photosensitizer → converted to protoporphyrin IX → activated by light (410–417 nm [blue], → ROS generation → necrosis/apoptosis. Tumor/precancer cells accumulate more porphyrins → effective for actinic keratoses and NMSCs.	Moderate efficacy	Sun/light sensitivity, changes in skin pigmentation (hypo- or hyperpigmentation), allergy to the photosensitizer, pain, possible systemic absorption, and local inflammation (swelling, blisters, crusting).
BF-200 ALA (Ameluz) gel plus red-light PDT*	Field-directed, FDA-approved	Topical photosensitizer → converted to protoporphyrin IX → activated by light 635 nm [red]) → ROS generation → necrosis/apoptosis. Tumor/precancer cells accumulate more porphyrins → effective for actinic keratoses and NMSCs.	Among highest efficacy for field therapy	Sun/light sensitivity, changes in skin pigmentation (hypo- or hyperpigmentation), allergy to the photosensitizer, pain, possible systemic absorption, and local inflammation (swelling, blisters, crusting).
MAL PDT*	Field-directed PDT	Topical photosensitizer → converted to protoporphyrin IX → activated by light 635 nm [red]) → ROS generation → necrosis/apoptosis. Tumor/precancer cells accumulate more porphyrins → effective for actinic keratoses and NMSCs.	Moderate efficacy	Sun/light sensitivity, changes in skin pigmentation (hypo- or hyperpigmentation), allergy to the photosensitizer, pain, possible systemic absorption, and local inflammation (swelling, blisters, crusting).
Daylight PDT (ALA or MAL)	Field-directed PDT variant	Topical photosensitizer → converted to protoporphyrin IX → activated by broad-spectrum visible daylight (380nm-780nm) → ROS generation → necrosis/apoptosis. Tumor/precancer cells accumulate more porphyrins → effective for actinic keratoses and NMSCs. Activated by daylight.	Equal to conventional PDT on face and scalp with less pain	Weather-dependent sun/light sensitivity, changes in skin pigmentation (hypo- or hyperpigmentation), allergy to the photosensitizer, pain, possible systemic absorption, and local inflammation (swelling, blisters, crusting).

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Destructive therapies				
Treatment	**Category**	**Mechanism of action**	**Effectiveness**	**Common adverse effects/limitations**
Cryotherapy (liquid nitrogen)	Lesion directed	Rapid freezing causes extra- and intracellular ice formation, followed by thaw-related vascular injury from vasoconstriction, reperfusion, and free-radical release.	Demonstrates cure rates of 57-98% for individual AKs	Pain, erythema, blistering, hypopigmentation, atrophy and hypertrophic scarring, and operator variability.
Curettage ± electrodessication	Lesion directed	Mechanical removal of dysplastic keratinocytes followed by heat generated by electrical current causing cellular destruction	Particularly effective for hyperkeratotic lesions with a recurrence rate of approximately 2%	Pain, scarring, infection, dyspigmentation, postoperative hemorrhage, and wound dehiscence.
CO_2 or Er:YAG ablative laser resurfacing	Field and lesion directed, older	Targets intracellular water as chromophore, causing rapid tissue heating and vaporization	Moderate-to-high efficacy for actinic keratoses, with complete clearance rates ranging from 72-78%	Erythema, hyperpigmentation, hypopigmentation, infection, and scarring.
Dermabrasion	Field directed, older	Mechanical removal of actinically damaged epidermis to the level of the papillary dermis	High efficacy, with 96% of patients remaining clear at 1 year	Hyperpigmentation, hypopigmentation, erythema, infection, and hypertrophic scarring.
Ablative fractional laser (AFXL) monotherapy	Field directed, not FDA-approved	Creates vertical microchannels of thermal injury that ablate abnormal epidermal tissue	Reduces AK burden from ~50-70% in studies	Pain, transient erythema, edema, pruritus, infection, and cost.
AFXL-assisted PDT (laser-assisted drug delivery)	Combination, not FDA-approved	Creates ablation channels, which increases ALA or MAL penetration before PDT	Higher clearance; ~70-90%	Erythema, crusting, hyperpigmentation, pruritus, cost, and technical skill.
Nonablative fractional lasers	Adjunctive, not FDA-approved	Creates columns of microscopic treatment zones, which induce microthermal injury zones, keratinocyte turnover, and rare direct necrosis of dysplastic cells	Variable results, less effective than AFXL	Erythema, edema, requires multiple sessions.

* 5-Aminolevulinic acid, methyl aminolevulinate

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