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Pigmentary Worsening During and After Tranexamic Acid Treatment for Melasma: A Scoping Review

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 July 2026 and was last updated on 12 July 2026.

INTRODUCTION

Review question / Objective Review question: What evidence is available regarding pigmentary worsening occurring during or after tranexamic acid treatment for melasma across all routes of administration and clinical settings?

Objective: This scoping review aims to map the extent, characteristics, and gaps in the evidence concerning pigmentary worsening among individuals receiving tranexamic acid for melasma. It will characterize the reported frequency, route and regimen of tranexamic acid administration, timing and clinical phenotype of worsening, terminology used, potential contributing factors, management, prognosis, and proposed mechanisms. It will distinguish on-treatment paradoxical worsening from post-treatment recurrence, relapse, or rebound hyperpigmentation and assess causal plausibility when sufficient patient-level information is available. Relevant registered trials and supplementary pharmacovigilance observations will be summarized separately.

Background Melasma is a chronic, relapsing hyperpigmentation disorder. Tranexamic acid is increasingly used for melasma through oral, topical, intradermal, and microneedling-assisted routes. Although it generally improves pigmentation, worsening during treatment or after discontinuation has occasionally been reported. Reported outcomes include paradoxical darkening, rebound hyperpigmentation, recurrence, and relapse. However, these outcomes may also reflect the natural course of melasma, ultraviolet exposure, inadequate photoprotection, injection-related inflammation, treatment failure, or concomitant procedures rather than a true adverse drug reaction. The available evidence is sparse, heterogeneous, and distributed across clinical studies, case-based reports, trial registries, and pharmacovigilance sources. This scoping review will map the evidence, clarify terminology, characterize clinical presentation and timing, examine management and prognosis, assess

causal plausibility when possible, and identify research gaps. Supplementary pharmacovigilance findings will be interpreted separately from clinical evidence.

Rationale Evidence on pigmentary worsening associated with tranexamic acid treatment for melasma is limited, inconsistently defined, and distributed across heterogeneous study designs and information sources. Recurrence, relapse, rebound hyperpigmentation, and paradoxical worsening may represent distinct clinical phenomena but are often reported interchangeably. A scoping review is therefore appropriate to clarify these concepts, map the types and extent of available evidence, characterize treatment routes and clinical outcomes, and identify knowledge gaps. This review may support more consistent adverse-event reporting and guide future clinical and pharmacovigilance research.

METHODS

Strategy of data synthesis MEDLINE via PubMed, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) will be searched from inception through July 13, 2026. Controlled vocabulary, where available, and free-text terms will cover melasma or chloasma; tranexamic acid or TXA; and pigmentary outcomes such as hyperpigmentation, darkening, worsening, paradoxical reaction, recurrence, relapse, and rebound. Search strategies will be adapted for each database and limited to English-language reports. Reference lists of included reports and relevant reviews will also be examined. WHO ICTRP will be searched using terms for melasma and tranexamic acid. WHO VigiAccess will be searched separately using tranexamic acid as the medicinal substance and relevant pigmentation-related adverse-reaction terms. Findings will be synthesized descriptively and grouped by study design, treatment route, timing, and pigmentary phenotype. Study-specific counts and proportions will be reported when suitable denominators are available, without statistical pooling. WHO ICTRP and VigiAccess findings will be presented separately; VigiAccess data will not be used to estimate incidence or establish causality.

Eligibility criteria Population: Individuals with diagnosed melasma who receive tranexamic acid by any route, including oral, topical, intradermal or intralesional injection, and microneedling-assisted delivery. No restrictions will be applied regarding age, sex, dose, treatment duration, or concomitant therapy.

Concept: Pigmentary worsening occurring during treatment or after tranexamic acid discontinuation, including worsening of preexisting melasma, paradoxical darkening, rebound hyperpigmentation, recurrence or relapse, and new-onset hyperpigmentation. Recurrence and relapse will be mapped separately and will not automatically be considered adverse drug reactions. A comparator will not be required.
Context: All countries, geographic regions, and clinical settings will be eligible.
Eligible sources will include randomized and nonrandomized trials, single-arm and before-and-after studies, cohort and case-control studies, case series, case reports, and other reports containing sufficient original clinical information. Cross-sectional studies will be eligible only when tranexamic acid exposure clearly preceded the outcome. Studies unrelated to melasma, those without extractable pigmentary outcomes, preclinical studies, reviews, editorials, guidelines, expert opinions, and reports without original patient data will be excluded. Eligibility will be restricted to English-language sources, without publication-date restrictions. Relevant WHO ICTRP records will be mapped separately.

Source of evidence screening and selection Records from bibliographic databases will be combined, and duplicates will be removed electronically and verified manually. After pilot testing the eligibility criteria, two reviewers will independently screen titles and abstracts. Reports considered potentially eligible by either reviewer will undergo independent full-text assessment. Disagreements will be resolved through discussion and consensus; unresolved disagreements will be adjudicated by a third reviewer. Reasons for full-text exclusion will be documented.
Multiple reports from the same study will be linked and treated as one study. WHO ICTRP records will be screened separately and matched with corresponding publications to prevent double counting. The selection process will be presented using a PRISMA flow diagram. WHO VigiAccess findings will not be included in study-selection counts because they represent aggregated pharmacovigilance data.

Data management Search records will be exported to reference-management software, combined, and deduplicated electronically with manual verification. Screening decisions, eligibility judgments, and reasons for full-text exclusion will be documented in structured spreadsheets. Data will be charted using a standardized, pilot-tested form, with separate sections for published studies, WHO ICTRP records, and WHO VigiAccess

findings. Search files, registry exports, and dated pharmacovigilance records will be retained to support reproducibility. All files will be version-controlled, backed up, and stored in password-protected institutional storage accessible only to the review team. No personally identifiable patient information will be collected.

Language restriction English.

Country(ies) involved Thailand.

Keywords melasma; tranexamic acid; hyperpigmentation; paradoxical worsening; rebound hyperpigmentation; pharmacovigilance.

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