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Pigmentary Worsening During Tranexamic Acid–Based 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 19 July 2026.

INTRODUCTION

Review question / Objective Review question: What clinical or measurement-based pigmentary worsening has been reported during tranexamic acid–based treatment for melasma, and what are its characteristics, timing, treatment context and potential contributing factors?

Objective: To identify and characterize positive reports of pigmentary worsening occurring during active TXA-based treatment for melasma. The review will map the clinical phenotype, TXA route and regimen, concurrent procedures, timing, reported event proportions, potential contributing factors and alternative explanations, management and clinical course. Temporal association will be distinguished from causal attribution. Recurrence or relapse occurring only after treatment cessation and studies reporting zero events will not be included in the positive-event evidence map.

Background Melasma is a chronic hyperpigmentation disorder commonly treated with tranexamic acid (TXA) administered orally, topically, by intradermal injection or through procedure-assisted delivery. Although TXA generally improves pigmentation, clinical and measurement-based worsening signals have occasionally been reported during TXA-containing treatment. Such worsening may reflect post-inflammatory hyperpigmentation from laser treatment, microneedling or injection trauma; ultraviolet or heat exposure; inadequate photoprotection; skin-barrier disruption; individual susceptibility; treatment failure; or natural fluctuation rather than a direct adverse reaction to TXA. The terminology, timing, measurement and causal interpretation of these events are inconsistent. A scoping review of positive reports is therefore needed to characterize the reported events, treatment contexts and potential contributing factors while distinguishing temporal association from causation.

Rationale Evidence concerning pigmentary worsening during TXA-based treatment for

melasma is heterogeneous and inconsistently reported. Clinical hyperpigmentation, objective increases in pigmentation scores and procedure-associated post-inflammatory hyperpigmentation may represent different phenomena, while temporal association with TXA does not establish causation. A positive-event scoping review is appropriate to map the types and contexts of reported worsening, clarify terminology, characterize treatment routes and concurrent procedures, examine potential contributing factors and identify evidence gaps. The review is not intended to estimate incidence, prevalence or pooled risk. Recurrence or relapse occurring only after treatment cessation and studies reporting zero events will therefore fall outside the revised scope.

METHODS

Strategy of data synthesis Scopus and PubMed/MEDLINE were searched from inception through July 2026 using controlled vocabulary, where available, and free-text terms for melasma or chloasma and tranexamic acid or TXA, without outcome-specific search terms. Bibliographic database searches were limited to English-language reports without publication-date restrictions. WHO ICTRP was searched separately for trials involving melasma and TXA, and relevant registry records were matched with publications to prevent double counting. WHO VigiAccess was searched separately as a supplementary pharmacovigilance source using tranexamic acid as the medicinal substance and pigmentation-related adverse-reaction terms. Eligible clinical evidence will be synthesized descriptively as a positive-event evidence map without meta-analysis or pooled incidence estimation. Reports will be assigned to four mutually exclusive treatment contexts: nonprocedural oral-containing regimens, nonprocedural topical regimens, intradermal or intralesional injection, and procedure-assisted TXA involving laser, microneedling or radiofrequency, with procedure-assisted classification taking precedence for combination treatments. Clinical pigmentary events will be distinguished from measurement-only worsening signals. The synthesis will describe study design, TXA regimen, concurrent treatments, number exposed, number experiencing worsening, study-specific event proportion where calculable, timing, phenotype, severity, potential contributing factors, management and clinical course. Reports without a participant-level numerator will be summarized narratively and excluded from event-proportion calculations. Causal plausibility will be discussed using temporality, comparator findings, alternative explanations, dechallenge or rechallenge information and the original authors' attribution. Study-specific proportions will not be combined into an overall incidence, prevalence or risk estimate. Eligible WHO ICTRP findings will be presented separately from published clinical evidence, while aggregated WHO VigiAccess findings will be reported as supplementary pharmacovigilance signals and will not be used to estimate incidence or establish causality.

Eligibility criteria Individuals with clinically diagnosed melasma who received tranexamic acid (TXA) by any route, including oral, topical, intradermal or intralesional injection, or procedure-assisted delivery, will be eligible without restrictions on age, sex, dosage, treatment duration or concomitant therapy. Eligible reports must document at least one positive clinical or measurement-based signal of new or increased pigmentation during active TXA-based treatment, including hyperpigmentation, post-inflammatory hyperpigmentation, worsening above baseline or an objective increase in pigmentation measurements. Events occurring during laser, microneedling, radiofrequency or injection procedures will be eligible when TXA formed part of the treatment regimen, although temporal association and causality will be evaluated separately. Eligible evidence will include primary clinical research such as randomized and nonrandomized trials, single-arm or before–after studies, cohort and case-control studies, case series and case reports. Studies reporting no pigmentary-worsening events, only recurrence or relapse after treatment cessation, residual melasma or inadequate improvement without increased pigmentation, worsening occurring only before TXA treatment, conditions other than melasma, insufficient relevant outcome information or no additional primary-outcome data will be excluded. Reviews, guidelines, editorials, expert opinions, protocols and secondary reports without additional relevant data will also be excluded. English-language evidence will be included without publication-date restrictions.

Source of evidence screening and selection Records from bibliographic databases were combined and deduplicated electronically with manual verification. Two reviewers independently screened titles and abstracts, and records considered potentially eligible by either reviewer proceeded to full-text assessment. The absence of a worsening outcome from the abstract alone was not used as a reason for exclusion when the report was otherwise potentially relevant. The same two reviewers independently assessed the full texts

using the revised eligibility criteria, with inclusion requiring at least one positive clinical or measurement-based pigmentary-worsening signal during active TXA-based treatment. Disagreements were resolved through discussion and consensus, and unresolved disagreements were adjudicated by a third reviewer. Reports describing zero events, recurrence or relapse only after treatment cessation, or no eligible pigmentary-worsening outcome were excluded, with one primary exclusion reason documented for each report. Multiple reports from the same study were linked, and secondary reports were retained only when they provided additional relevant primary-outcome data. Artificial-intelligence tools were used only to assist organization and cross-checking; all eligibility decisions were made or verified by the human reviewers. WHO ICTRP records were matched with corresponding publications to prevent double counting. WHO VigiAccess was treated as a supplementary pharmacovigilance source, and its aggregated findings were not considered individual studies or included in PRISMA selection counts. The selection process will be presented using a PRISMA 2020 flow diagram.

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.

Reporting results / Analysis of the evidence Results will be reported in accordance with PRISMA-ScR. The included evidence will be summarized descriptively and grouped into four mutually exclusive treatment contexts: nonprocedural oral-containing regimens, nonprocedural topical regimens, intradermal or intralesional injection, and procedure-assisted TXA involving laser, microneedling or radiofrequency. Clinical pigmentary events will be distinguished from measurement-only worsening signals. For each report, the study design, TXA regimen, concurrent treatments, number exposed, number experiencing worsening, study-specific event proportion where calculable, timing, phenotype, severity, potential contributing factors, management and clinical course will be presented. Reports without a participant-level numerator will be summarized narratively and excluded from event-proportion calculations. Because only positive-event reports are eligible, no pooled incidence, prevalence or risk estimate will be calculated. Causal plausibility will be discussed descriptively using temporality, comparator findings, alternative explanations, dechallenge or rechallenge information and the original authors' attribution, without assuming that temporal association establishes causation. WHO VigiAccess findings will be reported separately as aggregated suspected adverse-reaction data and will not be combined with clinical-study findings or used to estimate incidence or establish causality.

Presentation of the results Study selection will be presented using a PRISMA 2020 flow diagram showing the numbers of records identified, screened, assessed at full text, excluded with reasons and included in the review; WHO VigiAccess data will not be included in these counts. The findings will be presented as a positive-event evidence map and structured tables summarizing author, year, country, study design, sample size, TXA route and regimen, concurrent treatments or procedures, pigmentary-worsening phenotype, timing, numerator and denominator, study-specific event proportion where calculable, management, clinical course and causal interpretation. Results will be organized into nonprocedural oral-containing regimens, nonprocedural topical regimens, intradermal or intralesional injection, and procedure-assisted TXA, with clinical events distinguished from measurement-only signals. Study-specific proportions will be clearly identified as proportions within event-positive studies rather than incidence estimates. WHO VigiAccess findings will be presented separately as supplementary aggregated pharmacovigilance data.

Other relevant information Amendment dated 19 July 2026: Following preliminary screening and full-text assessment, but before final evidence synthesis and manuscript preparation, the scope was narrowed from pigmentary worsening during or after TXA treatment to positive clinical or measurement-based pigmentary-worsening signals occurring during active TXA-based treatment. Reports describing only recurrence or relapse after treatment cessation and studies reporting no worsening events were excluded because these represent conceptually different outcomes. Consequently, the review will provide a

positive-event evidence map and will not estimate pooled incidence, prevalence or risk. The title, review question, background, rationale, eligibility criteria, screening procedures, synthesis and presentation plans were revised accordingly. The original broad search terms remain suitable for identifying the revised evidence base, while the description of the search sources has been clarified to reflect the searches actually conducted. WHO VigiAccess will be retained solely as a supplementary pharmacovigilance source, reported separately from the included clinical studies and PRISMA selection counts. These post-registration changes will be disclosed transparently in the final review.

Language restriction English.

Country(ies) involved Thailand.

Keywords Melasma; tranexamic acid; pigmentary worsening; hyperpigmentation; post-inflammatory hyperpigmentation; adverse events; treatment-related complications; scoping review; pharmacovigilance.

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