Melasma is a common acquired disorder of pigmentation, typically presenting in a symmetrical fashion on photodamaged areas. It tends to respect orbital and mandibular margins, and often occurs in a cen-trifacial or malar distribution. Although the aetiology remains poorly under-stood, aberrant activation of melanocytes and underlying angiogenesis are thought to play a role.1,2 Predisposing factors include hormonal factors (including oral contra-ceptive, hormone replacement therapy, pregnancy), female sex and genetic susceptibility.

Treatment of melasma can be challenging for clinicians and frustrating for patients. Historically, this has comprised stringent photoprotection, topical agents (including hydroquinone, retinoids, corticosteroids, azelaic acid or combinations thereof) with a limited evidence base for lasers and chemical peels.

Recent attention has focussed on the usefulness of oral tranexamic acid (TA) in reducing the appearance of melasma. TA is an antifibrinolytic agent, used for the management of menorrhagia and to reduce bleed-ing post-trauma. TA has several reported uses in der-matology, notably for physical urticaria and hereditary angio-oedema. In melasma, postulated mechanisms of action of TA include reduction of angiogenesis, including reduced expression of vascular endothelial growth factor and endothelin-1,3 and inhibition of the plas-minogen/plasmin pathway, which in turn interferes with the interaction of keratinocytes and melanocytes, inhibiting melanin synthesis.

While there have been several case reports and exploratory case series of the use of oral TA for melasma, Lee et al. in 20141 took the highly informative step of publishing their experience in the largest retro-spective case series to date of 561 cases with clinical melasma treated with oral TA in the National Skin Centre, Singapore, a tertiary referral dermatology centre. Of note, the dose of TA used (250 mg twice daily, equalling 15 g/month) is less than the cumulative monthly dose of TA recommended for menorrhagia (up to 4 g for 4 days, equalling 16 g/month),4 suggesting that the proposed TA doses have been used safely for some time for other indications.

In that study, 1081 patients were identified as having been treated with oral TA (250 mg twice daily) for clinical melasma, of whom 561 had adequate assessment and follow-up documentation to be included in the case series. Extent of disease and response to treatment was gauged by Physician Global Assessment (PGA), undertaken at each visit.

Of the 561 patients reported, 91% were female and 9% were male. Median age of onset was 40 years (range 15–62 years) and median time between onset and seeking treatment was 7 months (range 0–40 months). Of the 561 patients, 530 completed the full course of prescribed treatment. Median duration of treatment was 4 months and median time to show improvement was 2 months. The majority of patients (503; 89.7%) showed clinical improvement, irrespective of whether concomitant topical therapies were used, while 56 (10.0%) had no improvement and 2 (0.4%) had worsened disease. More favourable responses to TA treatment were seen in patients with no family history of melasma and in patients with an older age of onset of melasma. On discontinuing treatment, 27.2% patients relapsed.

Adverse effects (AEs) were reported by 40 patients (7%), with the most common being abdominal pain (n = 12), headache (n = 6), menstrual irregularities (n = 4), tinnitus (n = 3), paraesthesia (n = 3) and nausea/vomiting (n = 2). One patient developed deep vein thrombosis: on later questioning, it emerged that
the patient had failed to disclose a known family history of venous thromboembolism, and was subsequently found to have protein S deficiency.

Clinicians should take a detailed personal and family history of risk factors for venous thromboembolism, heart disease and cerebrovascular disease before initiating therapy with TA. Contraindications to use of TA include hypersensitivity to the drug, active thromboembolic disease, history of venous or arterial thrombosis, fibrinolytic conditions following consumptive coagulopathy, severe renal impairment (risk of accumulation) and history of convulsions.4

Lee et al. rightly note that their study is a retrospective case note review and lacks an objective pigment measuring device or serial Melasma Area and Severity Index (MASI) scores. Another caveat is the generalizability of these findings to patients in other countries, as the Asian population in Singapore may not be representative of Asian populations elsewhere with respect to drug effectiveness and AE profile, particularly given differences in cardiovascular risk factors between East and South Asian populations.

A 12-week comparative study of intradermal microinjections of TA (4 mg/mL every 4 weeks; n = 50) vs. oral TA (250 mg twice daily; n = 50) suggested that both routes of administration could elicit comparable reductions in MASI.5 A subsequent review of all reported studies of TA for treatment of melasma identified only one study (of six) supporting the use of topical TA,6 and suggested that while intradermal TA injections may be helpful, the largest series required weekly injections for 12 weeks, which may limit its use for busy patients and clinicians.

Nonetheless, the titular paper of Lee and colleagues affords credibility to the off-label use of oral TA (250 mg twice daily) for up to 4 months as a well-tolerated, adjunctive treatment for melasma.

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CPD questions

Learning objective
To consolidate knowledge of the use of oral tranexamic acid for melasma.

Question 1
In the largest case series to date, what dose of systemic tranexamic acid was used for treatment of melasma?
(a) 250 mg once daily.
(b) 250 mg twice daily.
(c) 500 mg once weekly.
(d) 500 mg twice daily.
(e) 500 mg twice weekly.

Question 2
What was the most frequently reported adverse effect (AE) of treatment with oral tranexamic acid for melasma?
(a) Abdominal pain.
(b) Deep vein thrombosis.
(c) Headache.
(d) Menorrhagia.
(e) Nausea.

Instructions for answering questions
This learning activity is freely available online at http://www.wileyhealthlearning.com/ced
Users are encouraged to
• Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
• Reflect on the article
• Register or login online at http://www.wileyhealth learning.com/ced and answer the CPD questions
• Complete the required evaluation component of the activity

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

This activity will be available for CPD credit for 2 years following its publication date. At that time, it will be reviewed and potentially updated and extended for an additional period.