Facial pigmentation

Common causes and how to manage

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Facial pigmentation may be due to a generalised process but most often is localised to the face. Melasma and actinic damage pigmentation are common and tend to be bilaterally distributed and slowly progressive. Irregularly shaped isolated lesions should be viewed with more caution, and biopsy may be required. Treatments include topical and oral medications, peels, intense pulsed light therapy and laser treatment.

KEY POINTS

- Diagnosis of the type of facial pigmentation can be made on clinical grounds in most cases.
- Facial pigmentation is a cause of considerable psychosocial distress for many patients.
- Melasma, the most common facial hyperpigmentation worldwide, is most prevalent in women and people with constitutionally darker skin. It occurs in approximately 25% of women who are pregnant.
- Hydroquinone-based skin-bleaching preparations remain the gold standard for the treatment of melasma.
- Many patients with facial pigmentation can be managed in the general practice setting but referral for specialist management may be required for refractory cases.

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Around 14% of GP consultations are for the management of skin diseases.[1] Pigmentary disorders represent a large proportion of diagnoses in dermatological populations.[2] Melasma, the most common facial pigmentation worldwide, may account for up to 10% of new dermatology referrals,[3] and GPs therefore need to be able to recognise it.

Skin pigmentation normally varies according to racial origin and the amount of sun exposure, and pigmentation disorders are often more troublesome in constitutionally darker skin ('skin of colour'). Facial hyperpigmentation manifests as either localised to the face or part of diffuse disease. Pigmentation localised to the face usually represents a benign condition, although it may be the cause of significant psychological distress because of its high visibility and sociocultural implications (regardless of the nature of the problem, people generally desire uniformity of skin colour). Increased facial pigment can, however, herald underlying systemic disease or malignancy.

Melanin contributes to racial and phenotypic appearance, but also has important roles in protecting from ultraviolet (UV) radiation damage and scavenging of toxins. Several pigment intensifiers have been identified, the most notable of which are UV radiation and, in the setting of melasma, oestrogen and progesterone. The process of pigment intensification is thought to involve an increase in pigment production and/or melanocyte numbers, usually mediated, at least in part, by the enzyme tyrosinase. Several established treatments target this enzyme, although improved understanding of melanogenesis in recent times has seen the emergence of several novel treatment options.

This article reviews the causes of hyperpigmentation and discusses treatment options for facial pigmentation that can be used in general practice.

Generalised versus localised hyperpigmentation

Generalised hyperpigmentation may be drug-induced, nutrition-related, have endocrine or metabolic causes or occur after inflammation. It can also occur with malignancies or have genetic causes. Limited facial pigmentation, the most common presentation of localised hyperpigmentation, typically is part of several common and largely benign skin conditions. Solar lentigines (freckles), melasma and postinflammatory hyperpigmentation are some of the more common facial pigmentations (Box 1).

Generalised hyperpigmentation

The causes of generalised hyperpigmentation are listed in Box 2. Drug-induced hyperpigmentation may occur with use of minocycline and hormonal contraceptives. Nutrition-related hyperpigmentation may be seen with deficiencies of vitamin B12 or folate associated with inadequate dietary intake or gastrointestinal malabsorptive disease (e.g. Crohn's disease), and alcoholism is known to deplete folic acid stores. The endocrinopathies and metabolic disorders most commonly associated with systemic hyperpigmentation are Addison's disease, haemochromatosis and hyperthyroidism; although patients may have associated symptoms or a past medical or family history suggestive of these conditions, pigment changes are often among their first signs. Postinflammatory hyperpigmentation is not a common cause of 'generalised' hyperpigmentation. Far less frequently, occult malignancy such as adrenocorticotrophic hormone (ACTH)-producing lung carcinomas and metastatic melanomas may cause generalised hyperpigmentation.

Symmetrical distribution is a hallmark of hyperpigmentation caused by systemic disease. In patients with Addison's disease, hyperpigmentation is most intense on light-exposed areas, in skin creases and flexures, at sites of friction and on mucous membranes; other associated features of this disease are loss of androgen-stimulated hair, such as pubic and underarm hair. Patients with hyperthyroidism may display the Addisonian pattern of pigmentation but involvement of mucous membranes is uncommon and darkening of nipples and genital skin is less striking; the eyelids are occasionally pigmented and some patients show localised 'melasmal' rather than diffuse pigmentation.

1. COMMON FACIAL PIGMENTATIONS

- Melasma
- Postinflammatory
- Sun-damaged skin
- Photosensitivity
  - connective tissue disease
  - drugs
- Naevi
  - Ota
  - Hori
- Fixed macules
  - lentigines (solar and other)
  - seborrhoeic keratoses

2. CAUSES OF GENERALISED HYPERPIGMENTATION*

Drug and toxins
- Analgesics (NSAIDS)
- Antiarrhythmics (amiodarone)
- Antibiotics (tetracyclines [e.g. minocycline], co-trimoxazole)
- Anticonvulsants (phenytoin)
- Antidepressants (imipramine, desipramine)
- Antimalarial drugs (hydroxychloroquine, chloroquine)
- Cytotoxics (bleomycin, busulfan, cyclophosphamide, 5-fluorouracil)
- Heavy metals (arsenic, bismuth, gold, mercury, silver)
- Hormones (oestrogen, progesterone, adrenocorticotrophic hormone)
- Psychotropics (phenothiazines [e.g. chlorpromazine])

Postinflammatory
- Allergic dermatitis
- Autoimmune disorders such as systemic lupus erythematosus/scleroderma
- Inflammatory dermatoses such as acne, psoriasis
- Medication use (e.g. hydroquinone, tretinoin)
- Postinfective (e.g. tuberculosis, malaria, subacute bacterial endocarditis, HIV)
- Ultraviolet light (most frequent postinflammatory cause)

Nutritional
- Kwashiorkor
- Pellagra
- Scurvy
- Vitamin B12/folate deficiency (most frequent nutritional cause)

Endocrine
- Pregnancy
- Addison's/Cushing's disease (one of the most frequent endocrine causes)
- Phaeochromocytoma
- Carcinoid syndrome
- Hyperthyroidism (one of the most frequent endocrine causes)
- Acanthosis nigricans

Metabolic
- Chronic renal failure
- Chronic liver disease
- Haemochromatosis (most frequent metabolic cause)
- Porphyria

Malignancy
- Melanoma (rarely)
- Small cell lung carcinoma (rarely)

Genetic
- Familial (e.g. periorbital hyperpigmentation)
- Chromosomal (e.g. xeroderma pigmentosum; dyskeratosis congenital)
- Racial (e.g. naevi of Ota, Ito, Hori)

* Causes listed in alphabetical order.

TABLE 1. FITZPATRICK SKIN TYPES

Skin type	Skin/hair/eye colour; example ethnicity	Characteristics
I	White; very fair, red or blonde hair, blue eyes, freckles; Celtic	Always burns, never tans
II	White; fair, red or blond hair; blue, hazel or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair colour (common)	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin; Asian	Rarely burns, tans with ease
V	Dark brown; mid-eastern skin types, East Indian	Very rarely burns, tans easily
VI	Black; Aboriginal and Torres Strait Islander	Never burns, tans very easily

Patients with haemochromatosis have slate grey or brownish-bronze skin, mostly in sun-exposed areas and particularly on the face; other associated features include skin and nail changes such as hair loss and koilonychia (twisted nail plate).

Assessing localised hyperpigmentation

Diagnosis of the various facial pigmentations can be made on clinical grounds in most cases. Differential features can be identified using the following diagnostic schematic:

- skin type
- history
  - onset and duration
  - comorbidities
  - medication use
- examination
  - morphology
  - distribution.

Fitzpatrick skin type

Solar lentigines and other hyperpigmentations due to actinic (solar) damage are seen predominantly in people with Fitzpatrick skin types I to III, the predominant skin types in Australia, whereas melasma and postinflammatory hyperpigmentation are seen mainly in people of skin types III to VI (Table 1; Figures 1 and 2).[4,5]

Onset and duration

Naevus of Ota (pigmented dermal 'birthmark') exhibits a bimodal onset, presenting either at birth or puberty, whereas solar lentigines appear during childhood (Figure 3). Melasma onset spans the reproductive years from 20 to 40 years of age. Cutaneous systemic lupus erythematosus and naevus of Hori (also known as acquired bilateral naevus of Ota) similarly have broad spectrums of onset, appearing between the ages of 20 and 50 years, and 20 and 70 years, respectively. Actinic damage and seborrhoeic keratoses become apparent during the fourth decade of life and usually increase in number with age.

Comorbidities

A specific history should be sought regarding endocrinological and metabolic conditions associated with skin hyperpigmentation (Table 1).

Medication use

Hormonal contraceptive use commonly triggers melasma in women. Minocycline and phenytoin are other recognised causes of facial hyperpigmentation, and other parts of the body and mucosa may also be involved.[6]

Specific lesional characteristics such as colour (e.g. brown, grey, blue-grey) and distribution depend on the causative agent. In the case of minocycline-induced pigmentation, 'prototype' minocycline degradation products are chelated with iron taken up by macrophages and pigmented drug metabolites deposited in the skin. Minocycline also increases levels of melanin in epidermal and dermal macrophages.

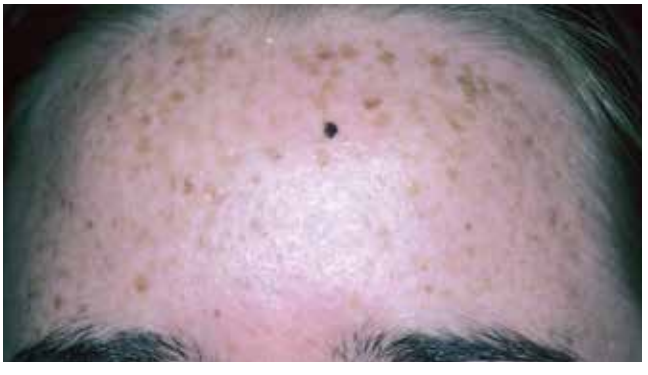

Figure 1. Freckles and an ink spot lentigo (also known as reticulated lentigo; occurs after sunburn in very fair skinned people).

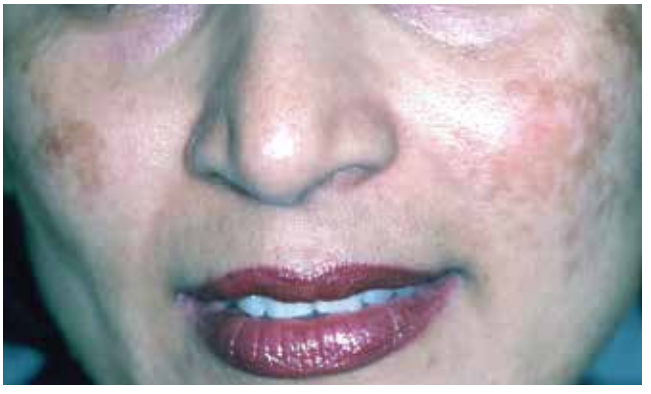

Figure 2. Melasma in type V skin.

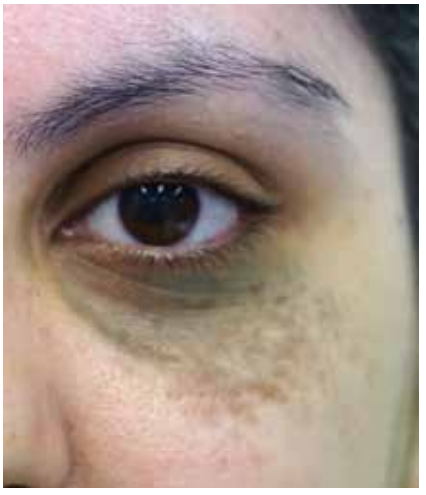

Figure 3. Naevus of Ota.

Pigment depth varies dependent on the drug, dose, duration of use and patient factors; biopsy may be useful for assessment.

Morphology

Facial pigmentation diseases may have macules varying in pigment intensity. Lentigines and melasma characteristically produce well-circumscribed lesions, whereas actinic damage and solar lentigines typically give a blotchy or speckled appearance (Figures 1 and 2). Seborrhoeic keratoses can sometimes resemble flat lentigines, but are distinguished by a characteristic waxy/scaly veneer. Naevi of Ota lesions sometimes coalesce forming larger patches (Figure 3).

Melanomas such as lentigo maligna are unilateral irregularly shaped lesions, often variegated in colour and architecture and best appreciated on dermoscopy (Figure 4). Timeline to invasion is variable and even invasive thin melanomas may evolve slowly.[7] Lesions diagnosed as a melanoma or considered a potential melanoma should always be biopsied or referred for confocal analysis.

Distribution

Lentigines (all types), melasma, photosensitive reactions and actinic elastosis are most typically found bilaterally on sun-exposed areas of the face, particularly the forehead and malar regions. Naevi of Ota are distributed unilaterally (rarely bilaterally) in the skin innervated by the first two branches of the trigeminal nerve, whereas naevi of Hori are bilaterally distributed. Naevi of Ota are most commonly found in people of Asian origin, and are uncommon in Caucasians.

Initial investigations for hyperpigmentation

Tests used in the initial investigation of generalised and facial hyperpigmentation are listed in Table 2.

Melasma

Melasma, often referred to as 'chloasma' or the 'mask of pregnancy,' is the most common facial pigmentation presentation worldwide, with a reported prevalence of about 6 to 9% in a Brazilian population-based study.[8] Women are affected nine times more often than men, and it occurs in about 25% of pregnant women. People with constitutionally darker skin (i.e. Fitzpatrick skin types III to VI) are affected more than people with light skin.

Clinically, it is an acquired progressive, nonscaling hypermelanosis of sun-exposed skin, chiefly affecting the face, more specifically the forehead, cheeks and chin regions.

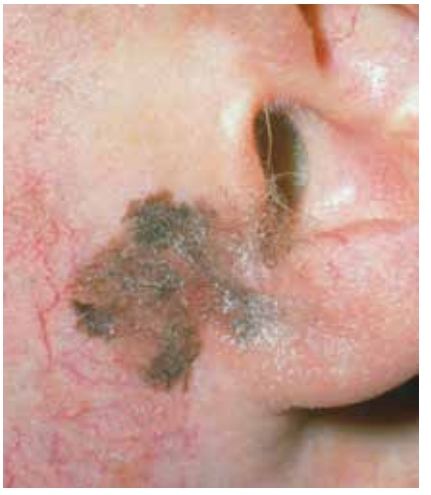

Figure 4. Lentigo maligna (preauricular region).

The pathophysiology of melasma is uncertain but an interplay of multiple inciting and exacerbating factors has been proposed. Genetic predisposition is suggested by a high reported incidence in family members in several studies. UV radiation, oestrogen and progesterone induce melanocyte proliferation, migration and melanogenesis independently and through upregulation of tyrosinase activity (Figure 5).[9] Hydroquinone, the mainstay of systemic treatment for melasma, and several other skin-lightening agents target tyrosinase primarily.

TABLE 2. INITIAL INVESTIGATIONS FOR HYPERPIGMENTATION

Cohort	Clinical suspicion	Indicated tests
Generalised hyperpigmentation without obvious aetiology	Nutritional cause	Measurement of levels of serum vitamin B12 and folic acid
	Endocrine cause	Measurement of levels of serum electrolytes, thyroid stimulating hormone, cortisol, adrenocorticotrophic hormone and, possibly, urinary catecholamines
	Metabolic cause	Serum liver and kidney function tests, iron studies
Localised facial hyperpigmentation where diagnosis is uncertain	Melanoma e.g. lentigo maligna	Punch biopsy, or excisional biopsy where possible
	Postinflammatory e.g. systemic lupus erythematosus	Examination for primary cutaneous inflammatory event such as drug reaction, connective tissue disease

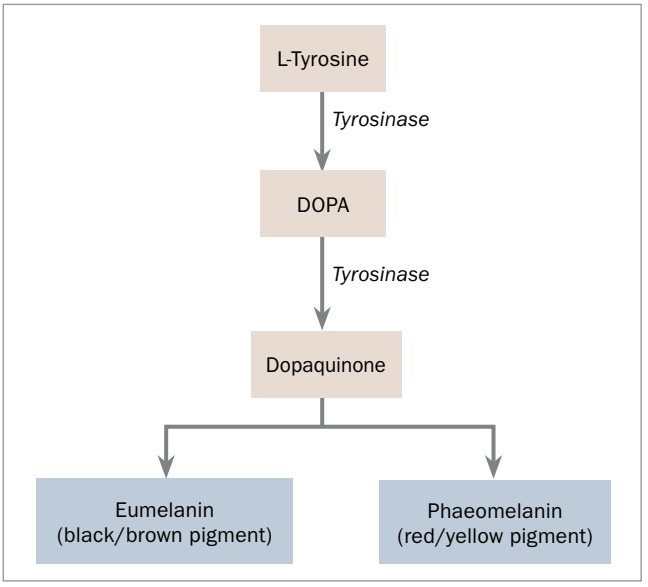

Figure 5. Tyrosinase-mediated reactions in the melanin production pathway.

Melasma is a chronic condition and recurrence is common, especially after re-exposure to sunlight. Intermittent, long-term topical therapy and strict sun protection are usually necessary to remain in remission. In some patients, areas of hyperpigmentation may never completely resolve.

Treatment of facial pigmentation

The management of the more common facial pigmentation disorders of melasma, lentigines, actinic damage and naevi are considered here. Although solar lentigines are a more common pigmentary problem than melasma in Australia, they are relatively straightforward to treat and so discussion will focus on the treatment of melasma, which remains a therapeutic challenge. All patients with melasma should be counselled about the condition's natural history and the management goals – 'control rather than cure'.

Treatment options for generalised pigmentation are diverse and aimed at managing its multiple causes, as previously listed, once the cause has been confirmed by investigation.

General measures

The first step in managing patients with skin pigmentation is to reduce and/or eliminate any triggers, such as cessation of the hormonal contraceptive in women with melasma.

All patients with facial pigmentation should be instructed to apply a broad-spectrum sunscreen (at least SPF 30+) containing a physical blocking agent (e.g. zinc oxide), backed by other sun protection measures including wearing a hat and long-sleeved clothing. The appropriate reapplication interval,

which may be up to two-hourly, should be guided by the risk pertaining to sun exposure and the nature and level of outdoor activity.

Cosmetic camouflage provides photoprotection as well as aiding cosmesis; a few commercially available products are listed in Box 3. When camouflage is not worn, sunscreen should be used.

Topical therapies

Hydroquinone

The main therapy for melasma is the skin-lightening agent hydroquinone. This benzene metabolite exerts multimodal effects through competitive inhibition of tyrosinase-mediated melanin production, degradation of melanosomes and inhibition of nucleic acid synthesis. It is used in varying concentrations, with 4% appearing to be most advantageous. Improvement is usually evident after 5 to 7 weeks, although treatment can be safely continued for up to 12 months.[10] Hydroquinone is most commonly used, and potentially best utilised in combination with other agents including retinoids (e.g. tretinoin) and corticosteroids (e.g. fluocinolone) to reduce side effects of each individual ingredient.[10]

Side effects reported as mild and transient include irritation, erythema, irritant or contact dermatitis and halo hypochromia. Rarer longer-term reactions include milia and postinflammatory hyperpigmentation. Initial concerns about the breakdown products of hydroquinone causing bone marrow toxicity and antiapoptotic effects are unsupported by more recent clinical research.[11]

Retinoids

The acne treatments tretinoin and adapalene have been shown to reduce epidermal pigmentation in melasma as monotherapy (off label use).[12,13] Adapalene is the first choice because it shares similar efficacy with its peers but is generally better tolerated.[13] Tazarotene may offer slightly superior results in postinflammatory hyperpigmentation (e.g. acne).[14] Unfortunately, retinoids can take up to 24 weeks to show effects so are best used in combination with other agents that

3. EXAMPLES OF COMMERCIALLY AVAILABLE COSMETIC CAMOUFLAGE PRODUCT BRANDS

- Dermablend (Vichy Laboratories)
- CM Beauty (formerly Covermark)
- Microskin (Microskin International Pty Ltd, Brisbane)
- Cover FX (Cover FX skin care)

have quicker effects (i.e. hydroquinone and fluocinolone). Retinoid products should be avoided in pregnancy because of the potential for teratogenicity.

Azelaic acid

Azelaic acid monotherapy has proven value in treating melasma (off label use) and postinflammatory hyperpigmentation such as that caused by acne. In a randomised, double blind study, 20% azelaic acid was shown to be as effective as hydroquinone 4% in the treatment of melasma, but without its side effects.[15] In the event of adverse effects, patients might be instructed to reduce dosing intervals and/or cease use temporarily, reintroducing when the effects have resolved.

Ascorbic acid

Topical ascorbic acid (vitamin C) is modestly effective as monotherapy for melasma but much less so than hydroquinone. Ascorbic acid has a superior safety profile however, and therefore may be of use in people who cannot tolerate hydroquinone.[16] It is available in many over-the-counter cosmeceuticals, both as monotherapy and in combination with other agents.

Combination therapy

Retinoid, hydroquinone and fluocinolone combination therapy produces the best and longest-lasting results of any commercially available topical agents for the treatment of melasma.[17] A combination skin-bleaching product is marketed as Tri-Luma (hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01%) in the USA but is not approved for use in Australia. Safety concerns were exaggerated in the early stages of its use, curbing interest.[18] Tri-Luma can be accessed on private prescription through compounding chemists.

Tranexamic acid

Tranexamic acid (TXA) has been reported as a promising potential treatment for melasma. It is thought to inhibit the plasminogen–plasmin system, interfering with the keratinocyte–melanocyte interaction.

TXA is being used in an oral form as limited duration therapy by some dermatologists in Australia for melasma that has not responded to topical agents (off label use).[10] The most commonly reported side effects are headaches, GI upset and hypomenorrhoea. Rare instances of thromboembolism, pulmonary embolus and myocardial infarction advocate for a cautious approach in people with hypercoagulable states (e.g. smokers, those who are obesity, those with a past history of thromboembolic disease) and those with comorbidities (e.g. hypertension) and of advanced age.[19] With future examination, it may become part of the GP's armamentarium for treating melasma but at this stage consideration warrants referral to a dermatologist.

'The main therapy for melasma is the skin-lightening agent hydroquinone.'

Physical therapies

Chemical peels

Chemical peels have variable success in reducing skin pigmentation and multiple treatments are usually required to achieve modest results. They are best used in combination with topical agents such as hydroquinone 4%.

Low concentrations of alpha-hydroxy acids such as glycolic, lactic and salicylic are most commonly used. Glycolic acid (20 to 30%) may be best for solar damage hyperpigmentation and people with types I or II skin.[20] Salicylic acid (20 to 30%) has been shown to be particularly beneficial for melasma and postinflammatory hyperpigmentation in patients with dark skin.[21] Patients must be forewarned about the risks of erythema, irritation, burning and, less commonly, postinflammatory hyperpigmentation and scarring.

Specialist referral is recommended for medium and deep chemical peels like trichloroacetic acid and phenol, respectively.

Dermabrasion

Dermabrasion is not popular as a treatment for facial pigmentation due to long downtimes and poor results.

Light therapies

Phototherapy for skin disorders carries an inherent risk of postinflammatory hyperpigmentation, and light and lasers should be used with extreme caution. Patients must be well versed in the risks. A test patch is recommended prior to initiation of treatment, especially in patients with types IV, V or VI skin. Lasers and energy devices are second-line treatment and only considered when topical therapies have not been suitably effective. In Australia, GPs, specialists, skin clinics and beauticians perform light treatments.

Intense pulsed light therapy. Intense pulsed light (IPL) technology is replacing laser as the standard first-line treatment in photodamage. This transition is credited to improved efficacy coupled with comparatively less downtime. Lentigines are among the many examples of pigmented lesions that have been successfully treated. Concomitant use of a Nd:YAG (neodymium-doped yttrium aluminium garnet) laser provides additional benefit with no additional downtime.[22]

IPL has also been used adjunctively with varied success in melasma; trials have reported almost universal recurrence however, perhaps directing best use at disease refractory to topical therapy alone.[23] Broadband light (BBL), which utilises a spectrum of nonablative and visible light, has shown similar benefits in photodamage, particularly for lentigines and epidermal dyspigmentation. Its effects may be augmented when used in combination with a Er:YAG (erbium-doped yttrium aluminum garnet) laser.[21]

Fractional photothermolysis. Er:YAG and carbon dioxide (CO_2) fractional lasers (the

laser beam is divided into thousands of microscopic treatment zones that target a fraction of the skin at a time) are effective for actinic damage and lentigines but should be considered second line, Er:YAG for superficial or mild damage and CO_2 for deeper photodamage.[25]

Fractional lasers are approved in some countries (e.g. the USA) for the treatment of melasma but are not routinely used because any short-term improvement is outweighed by the risk of causing other pigment problems.

Other. Q-switched lasers and combined Er:YAG/CO_2 lasers have either never shown benefit or have been associated with unsatisfactory adverse effects or superseded by more efficacious and/or practical treatments.

Conclusion

Facial pigmentation may be due to a generalised process but most often is localised to the face. The common melasma and actinic damage pigmentations tend to have a bilateral distribution and be slowly progressive. Irregularly shaped isolated lesions should be viewed with more caution, and biopsy may be required to exclude melanoma. Treatments include topical and oral medications and physical therapies such as peels, intense pulse light therapy and lasers. MT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: None.

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