Abstract
Melasma is one of the most common hyperpigmentary disorders found mainly in women and dark-skinned patients. Sunlight, hormones, pregnancy, and genetics remain the most implicated in the causation of melasma. Although rather recalcitrant to treatment, topical agents such as hydroquinone, modified Kligman’s Regime, azelaic acid, kojic acid, Vitamin C, and arbutin still remain the mainstay of therapy with sun protection being a cornerstone of therapy. There are several new botanical and non-botanical agents and upcoming oral therapies for the future. There is a lack of therapeutic guidelines, more so in the Indian setup. The article discusses available evidence and brings forward a suggested treatment algorithm by experts from Pigmentary Disorders Forum (SPF) in a collaborative discussion called South Asian Pigmentary Forum (SPF).

**Key Words:** Expert group, medical treatment, melasma

**What was known?**
- Medical management of melasma with topical hydroquinone or triple combination cream is the most effective treatment of melasma, although the last decade or more has seen a lot of side effects due to corticosteroids or hydroquinone if used unsupervised in Indian patients.
- Azelaic acid and kojic acid and vitamin C topically, though weaker agents, offer an alternative to hydroquinone containing creams.
- An initial evaluation and treatment of medical factors, photoprotection and triple combination cream works well and should be rotated with other non-hydroquinone containing agents.

**Introduction**
Melasma is a common acquired pigmentary skin disorder characterized by a symmetrical macular pigmentation of sun-exposed areas like the face. The three major patterns of pigmentation in melasma are centrofacial (cheeks, forehead, upper lip, and nose), malar (cheeks and nose), and mandibular (mandibular area of cheeks). Melasma affects females much more commonly than males and majority of patients are in the third and fourth decades of their life. Several factors such as genetics, sunlight, cosmetics, pregnancy, hormonal treatments, thyroid dysfunction, and drugs have been implicated in the pathogenesis of melasma.

The treatment of melasma includes various topical and/or systemic agents. The aim of this article is to review the evidence available from the existing literature on prevalence and predisposing factors of melasma and suggest management guidelines for this common yet challenging skin disorder. This article discusses available evidence and brings forward a suggested treatment algorithm by 15 experts from Pigmentary Disorders Society (PDS) in a collaborative discussion called South Asian Pigmentary Disorders Forum (SPF).
Methods
A panel comprising of 15 eminent dermatologists from across the country with vast experience and significant academic contribution toward melasma was formed. These were experts from Pigmentary Disorders Society (PDS) in a collaborative effort called South Asian Pigmentary Disorders Forum (SPF).

This was followed by an extensive literature search from the database-PUBMED and COCHRANE LIBRARY. The keywords used for the search were melasma, treatment, management, hydroquinone (HQ), retinoids, sunscreens, oral drugs, safety, triple combination, chemical peels, and lasers. The articles published in the past two decades were included in the study. However, few older publications were included to describe the evolution of treatment over the years. Poorly designed studies and those with conflicting results were excluded from the study. This was followed by day panel discussion during which the opinion of the panellists was sought and recorded.

Findings
Prevalence and predisposing factors
The reported prevalence of melasma is variable and is based on the population group studied. It ranges from 8.8% among Latino males to 40% in Southeast Asian populations. In a prospective study conducted by Sarkar et al. in a tertiary care hospital in India, the prevalence of melasma was found to be 20.5% in men. Melasma, however, affects women more commonly than men.

The major etiological factors involved in melasma are genetic susceptibility, sun exposure, and hormones. Ortonne et al. conducted a larger global survey in 324 women with melasma and found that 50% of patients had a family history of melasma in at least one family member. The most common time of onset of melasma was post pregnancy (42%), whereas 26% of patients developed it during pregnancy. In another study carried out by Tamega Ade et al. in 302 Brazilian patients with melasma, it was found that the most common precipitating factors were pregnancy (36.4%), oral contraceptives (16.2%), and sun exposure (27.2%).

The frequency of thyroid disorders is four times greater in patients with melasma. In a study conducted by Lutfi et al., thyroid abnormalities were found in 58.3% of melasma patients. In a recent Indian study conducted by Gopichandani et al. in melasma patients, levels of luteinizing hormone, estradiol, and progesterone were lower in cases compared to controls indicating a suppression of hypothalamic-gonadal axis in these patients. Other factors that could contribute include: estrogens such as estriol and estrone, overexpression of estrogen receptors or increased responsiveness to circulating estrogens. The study also found low testosterone in patients as compared to the control group, again pointing toward a suppressed gonadal function.

Important/key points
- There is a paucity of community-based studies documenting the prevalence of melasma. Majority of currently available literature and statistics are from hospital-based studies
- Sun exposure and hormonal stimuli in a genetically predisposed individual can lead to the development of melasma
- More studies needed to validate the association between hormones and melasma.

Sun protection for melasma
There is sufficient literature to prove that light from both ultraviolet (UV) and visible spectrum is involved in the pathogenesis of melasma. To assess the efficacy of sunscreens in preventing the development of melasma, Lakhdar et al. conducted a study in 200 Moroccan females who were <3 months pregnant. They were asked to use a sunscreen with Sun Protection Factor (SPF) of 50+ and UVA protection factor of 28 during the day, and it was seen that only 2.7% of these women developed melasma during pregnancy.

Boukari et al. in a prospective randomised controlled trial (RCT), conducted in 40 patients with melasma, established the efficacy of sunscreen with combined protection against UV and short wavelengths of visible light (VL) in preventing melasma relapses. Both the treatment groups contained the same filters against UV except that one group received formula containing iron oxides (Visible light absorbing pigment) also. The other group had a significant increase in melasma area severity index (MASI) from baseline to month 6, as compared to the one having the additional iron oxide, hence emphasizing the role of VL in the pathogenesis of melasma.

This was further confirmed in a study by Castanedo-Cazares et al. in a double-blind RCT in 68 patients with melasma to assess the efficacy of sunscreen with broad-spectrum UV protection containing iron oxide compared with a regular UV-only broad-spectrum sunscreen. Patients applied HQ as a depigmenting agent and were assessed by MASI, colorimetry and histologic analysis. The group that used UV-iron oxide sunscreen had greater improvements than the UV-only group. Hence, the depigmenting efficacy of HQ was enhanced with concomitant sunscreen use.

In a double-blind, placebo-controlled RCT by Vázquez and Sánchez, among 53 patients who concomitantly used 3% HQ with sunscreen, nearly 96.2% of patients showed improvement as compared to 80.7% of those using a placebo. Thus, a broad spectrum sunscreen not only prevents relapses of melasma but also enhances the efficacy of other topical therapies.
Based on the available literature, the following recommendations can be made for the use of sunscreens [Table 1]. The authors strongly believe that sunscreens should be prescribed to all patients of melasma, as it has been shown to be effective in reducing pigmentation following sun exposure.

**Role of camouflage**

It can take a long time for the patient to see results with the treatment prescribed, during which the option of cosmetic camouflage should be offered. There are several options available in various shades to suit the skin tone. It is important to choose easy-to-blend formulas that are nonirritating and provide smooth coverage.

**Topical treatment**

**Phenolic compounds**

**Hydroquinone**

HQ is the prototype depigmenting agent used in melasma that exerts its effect by inhibiting tyrosinase, the rate-limiting enzyme in melanin synthesis. HQ also affects the membranous structures of melanocytes and causes their apoptosis.

HQ 2%–4% is prominently used as mono-therapy and is summarized in Table 2.[11-20]

In a controlled study (n = 56), both 2% and 5% HQ creams were found to be equally effective, and marked improvement was recorded in 80% of the patients.[21] However, few inflammatory reactions occurred with the former. Concentration more than 5% may cause more irritation and worsening of hyperpigmentation in the form of exogenous ochronosis on prolonged use.

Pigment lightening by HQ becomes evident after 5–7 weeks of the treatment and is recommended to be continued for at least 3 months and up to 1 year.[22]

**Hydroquinone in dual combination**

HQ has been used in combination with other topical agents such as tretinoin and glycolic acid. Retinoids inhibit the transcription of tyrosinase thereby inhibiting melanogenesis. The studies summarising the use of HQ in dual combination have been listed in Table 3.[21-26]

**Triple combination**

One of the first combination topical therapies developed for the treatment of hyperpigmentation was the Kligman–Willis formula, consisting of 5% HQ, 0.1% tretinoin, and 0.1% dexamethasone.

The theory behind the effectiveness of this combination of agents is that tretinoin prevents the oxidation of HQ and improves epidermal penetration while the topical corticosteroid (TCS) reduces irritation due to the other two ingredients and decreases cellular metabolism, further inhibiting melanin synthesis.

To suit different skin types, the original Kligman’s formula has been modified in many ways through addition/alteration of one or more of its components. Maximum experimentation has been done with the TCS component, namely, the addition of mid to high potent, fluorinated/non fluorinated agents and their concentration. Furthermore, the concentration of tretinoin and HQ has been kept low in most formulations. Combination regimes are found to be more efficacious and faster acting than monotherapies, thereby shortening the treatment duration and reducing the AE due to an individual drug.

The synergistic action of the three topical agents achieves significantly higher depigmentation than either agent alone. According to a Cochrane Collaboration Review (2010), the triple-combination cream (TCC) having 4% HQ, 0.05% tretinoin, and 0.01% fluocinolone acetonide was significantly more effective in lightening melasma than HQ alone (relative risk [RR] 1.58, 95% confidence interval [CI] 1.26–1.97) or when compared to the dual combinations of tretinoin and HQ (RR = 2.75, 95% CI 1.59–4.74), tretinoin, and fluocinolone acetonide (RR = 14.00, 95% CI 4.43–44.25), or HQ and fluocinolone acetonide (RR = 10.50, 95% CI 3.85–28.60). Table 4 summarises the studies which have evaluated the role of triple combination cream in melasma.[27-32]

**Triple combination cream in long-term and maintenance treatment of melasma**

Melasma is a persistent disorder of pigmentation and relapse after initial improvement is common. Development of a maintenance regimen after initial improvement would help in the management.

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**Table 1: Recommendations for use of sunscreens**

| Serial No. | Recommendations |
|------------|-----------------|
| 1          | Patients of melasma require a broad spectrum SC (with SPF of at least 30) which covers UVA, UVB and VL |
| 2          | Inorganic SCs are preferred as they provide protection from the entire spectrum especially those containing iron oxide. Additionally, they provide a camouflage effect. Since inorganic alone in high concentrations are not cosmetically acceptable, a blend of inorganic and organic is the best. Those patients who would like a less visible SC, only organic SCs should be prescribed |
| 3          | The SC needs to be applied liberally (teaspoon rule) and repeatedly throughout the day (every 2-3 h). It needs to be emphasized to the patient that they should continue to use SC even when they stay indoors, and infrared light can also aggravate melasma |
| 4          | A note should also be made of the coexistent conditions in the patient like acne and general hydration of skin, occupation, needs and expectations from the product prescribed |

**Table 2:**

| Serial No. | Recommendations |
|------------|-----------------|
| 1          | Patients of melasma require a broad spectrum SC (with SPF of at least 30) which covers UVA, UVB and VL |
| 2          | Inorganic SCs are preferred as they provide protection from the entire spectrum especially those containing iron oxide. Additionally, they provide a camouflage effect. Since inorganic alone in high concentrations are not cosmetically acceptable, a blend of inorganic and organic is the best. Those patients who would like a less visible SC, only organic SCs should be prescribed |
| 3          | The SC needs to be applied liberally (teaspoon rule) and repeatedly throughout the day (every 2-3 h). It needs to be emphasized to the patient that they should continue to use SC even when they stay indoors, and infrared light can also aggravate melasma |
| 4          | A note should also be made of the coexistent conditions in the patient like acne and general hydration of skin, occupation, needs and expectations from the product prescribed |

**Table 3:**

| Serial No. | Recommendations |
|------------|-----------------|
| 1          | Patients of melasma require a broad spectrum SC (with SPF of at least 30) which covers UVA, UVB and VL |
| 2          | Inorganic SCs are preferred as they provide protection from the entire spectrum especially those containing iron oxide. Additionally, they provide a camouflage effect. Since inorganic alone in high concentrations are not cosmetically acceptable, a blend of inorganic and organic is the best. Those patients who would like a less visible SC, only organic SCs should be prescribed |
| 3          | The SC needs to be applied liberally (teaspoon rule) and repeatedly throughout the day (every 2-3 h). It needs to be emphasized to the patient that they should continue to use SC even when they stay indoors, and infrared light can also aggravate melasma |
| 4          | A note should also be made of the coexistent conditions in the patient like acne and general hydration of skin, occupation, needs and expectations from the product prescribed |

**Table 4:**

| Serial No. | Recommendations |
|------------|-----------------|
| 1          | Patients of melasma require a broad spectrum SC (with SPF of at least 30) which covers UVA, UVB and VL |
| 2          | Inorganic SCs are preferred as they provide protection from the entire spectrum especially those containing iron oxide. Additionally, they provide a camouflage effect. Since inorganic alone in high concentrations are not cosmetically acceptable, a blend of inorganic and organic is the best. Those patients who would like a less visible SC, only organic SCs should be prescribed |
| 3          | The SC needs to be applied liberally (teaspoon rule) and repeatedly throughout the day (every 2-3 h). It needs to be emphasized to the patient that they should continue to use SC even when they stay indoors, and infrared light can also aggravate melasma |
| 4          | A note should also be made of the coexistent conditions in the patient like acne and general hydration of skin, occupation, needs and expectations from the product prescribed |

**Table 5:**

| Serial No. | Recommendations |
|------------|-----------------|
| 1          | Patients of melasma require a broad spectrum SC (with SPF of at least 30) which covers UVA, UVB and VL |
| 2          | Inorganic SCs are preferred as they provide protection from the entire spectrum especially those containing iron oxide. Additionally, they provide a camouflage effect. Since inorganic alone in high concentrations are not cosmetically acceptable, a blend of inorganic and organic is the best. Those patients who would like a less visible SC, only organic SCs should be prescribed |
| 3          | The SC needs to be applied liberally (teaspoon rule) and repeatedly throughout the day (every 2-3 h). It needs to be emphasized to the patient that they should continue to use SC even when they stay indoors, and infrared light can also aggravate melasma |
| 4          | A note should also be made of the coexistent conditions in the patient like acne and general hydration of skin, occupation, needs and expectations from the product prescribed |

**Table 6:**

| Serial No. | Recommendations |
|------------|-----------------|
| 1          | Patients of melasma require a broad spectrum SC (with SPF of at least 30) which covers UVA, UVB and VL |
| 2          | Inorganic SCs are preferred as they provide protection from the entire spectrum especially those containing iron oxide. Additionally, they provide a camouflage effect. Since inorganic alone in high concentrations are not cosmetically acceptable, a blend of inorganic and organic is the best. Those patients who would like a less visible SC, only organic SCs should be prescribed |
| 3          | The SC needs to be applied liberally (teaspoon rule) and repeatedly throughout the day (every 2-3 h). It needs to be emphasized to the patient that they should continue to use SC even when they stay indoors, and infrared light can also aggravate melasma |
| 4          | A note should also be made of the coexistent conditions in the patient like acne and general hydration of skin, occupation, needs and expectations from the product prescribed |
| References                      | Study type | Number of patients | Treatment mode               | Treatment duration, follow up | Method of assessment | Results                                                                 | Adverse effects                  |
|--------------------------------|------------|--------------------|------------------------------|------------------------------|----------------------|-------------------------------------------------------------------------|----------------------------------|
| Haddad et al., 2003[11]        | R, DB, SF  | 30 (25 completed study) | Group 1: 4% HQ versus Placebo | 3 months Follow up - nil      | Clinical evaluation    | Improvement: Overall - 72%, HQ (76.9%) > skin whitening complex (66.7%) Statistically nonsignificant | Group 1: 25% AE (irritation) Group 2: None |
|                                |            | Divided into 2 groups | Group 2: Skin whitening complex 5% versus placebo Application on either half of face Daily SC (SPF25) in both groups |                              |                      |                                                                         |                                  |
|                                |            | Fitzpatrick skin type-IV–VI |                              |                              |                      |                                                                         |                                  |
| Monteiro et al., 2011[12]      | O, NR      | 60 patients Indian | 4% HQ versus KA 0.75% + 2.5% Vitamin C Daily SC SPF15 in both groups | 3 months Follow up - nil      | MASI                 | HQ cream superior to KA                                                | 6.7% AE (erythema and mild burning sensation) HQ 3.3% AE (erythema) with KA AE with HQ-AA |
| Farshi, 2011[13]               | R, O       | 29 patients, Middle-east | 4% HQ versus 20% AA twice daily | 2 months Follow up-nil        | MASI                 | AA significantly better than HQ                                       |                                  |
| Baliña and Graupe, 1991[14]    | R, DB      | 329 Epidermal or mixed melasma | 4% HQ versus 20% AA | 24 weeks Follow up-nil        | Planimetry (size) 5 point scale (pigment intensity) | Superior results with HQ (73%) as compared to AA (65%) |                                  |
| Piquero Martín et al., 1988[15] | R, DB, O  | 60 patients | 4% HQ versus 20%AA | 24 weeks Follow up-nil        | Clinical photography | HQ > AA                                                                 | Transient, mild to moderate irritant reaction in both groups |
| Verallo-Rowell et al., 1989[16] | R, DB      | 155 patients Indo-Malay-Hispanic origin | 2% HQ versus 20% AA Twice daily application Broad spectrum SC | 24 weeks Follow up-nil |                                     | Good to excellent results in AA (73%) > HQ (19%) | 68.7% with HQ and 6.2% with ASCA |
| Espinal-Perez et al., 2004[17]  | R, O       | 16 women Mexican | 4% HQ versus 5% ASCA Broad spectrum SC | 16 weeks Follow up-nil | Colormetry, digital photography, subjective evaluation MASI, mexameter | Superior results with Rumex occidentalis as compared to HQ |                                  |
| Mendoza et al., 2014[18]       | R, DB, placebo - controlled | 45 patients Skin type IV Epidermal and mixed melasma | 3% Rumex occidentalis versus 4% HQ | 8 weeks Follow up-nil |                              |                                                                         |                                  |

Contd...
There are controversies regarding the safety of use of TCS based TCC in long-term treatment of melasma. Apart from a few studies on fluocinolone based TCC, there is a dearth of studies evaluating the safety of TCC for long-term use. There are three studies where TCC has been used as a maintenance treatment for melasma Table 5.\textsuperscript{[33-35]}

The studies in Table 5 show that fluocinolone based TCCs can be used as maintenance regimen for more than 8 weeks up to a maximum period of 1 year in either daily/intermittent/tapering dose regimen. Adverse effects such as skin atrophy and telangiectasia were found to be quite low even on continuing this regimen for more than 6 months. However, daily treatment in the long term is associated with more AE while intermittent therapy was associated with higher relapse of melasma in one study.\textsuperscript{[35]}

In one RCT, objective reduction of melanin and presence of erythema was assessed in patients receiving maintenance therapy following initial 8 weeks of the treatment regimen. Using narrowband reflectance spectrophotometer, it was shown that there was no difference between melanin levels in the melasma lesions in patients following either twice weekly or tapering regimen.\textsuperscript{[36]} Adverse effects were rare in both phases of the study. There was borderline reduction in erythema with the tapering regimen.

**Triple combinations using mid-potent corticosteroid**

Triple combination using mometasone furoate as the steroidal component was quite popular in our country until recently. Despite the paucity of supporting evidence regarding the efficacy and safety of the combination, it has been used rampanty in the last decade, both as physician’s prescription and over-the-counter drug. This indiscreet usage has resulted in a number of AE in many patients.

In a retrospective study performed on 60 Indian patients of melasma who had used a mometasone-based TCC for at least 3 weeks over the past 1 year, it was found that majority (51.7%) of the patients had used it well beyond the recommended period.\textsuperscript{[37]} More than half of the patients showed steroid-related AE such as atrophy (19/60), telangiectasia (26/60), hypertrichosis (17/60), and acneiform eruption (11/60) while using this treatment for more than 2 months and almost all the patients were affected when they used it beyond 6 months. In addition, one-third of the patients complained of worsening of pigmentation and the rest claimed that their disease was the same as before and no patient rated his/her disease as better than what he/she had before the initiation of treatment. Furthermore,
there were complaints of an increase in the area of skin involvement that had occurred after stoppage of the TCC. Thus, triple combination topical therapy using low potent TCSs should be used. If properly supervised, this can be an effective drug in keeping the pigmentation under control.
Important points

- HQ alone in a concentration of 2% to 5% can be used as an effective monotherapy. It is found to be more efficacious than KA and AA. 4% HQ has been found to be more efficacious than 2% HQ as compared to 20% AA in most of the studies. Pigment lightening is observed in 3–6 months time. Higher of HQ is associated with increased risk of inflammatory response and long-term use may give rise to AEs like exogenous ochronosis.

- Table 6 lists the level and quality of evidence of use of HQ as monotherapy and in combination with other agents.

- While there has been a shift from the original Kligman’s regimen, the most well-studied formulation is that of 4% HQ, 0.05% tretinoin, and 0.01% FA. It has level A quality of evidence in treating melasma and is approved by the US FDA.

- When used daily for about 2 months, it results in clearing or near clearing of lesions in several well-designed RCTs.

- Long-term therapy with TCC for more than 6 months,

### Table 5: Summary of studies evaluating the long term safety of triple-combination cream in melasma

| Reference                  | Type of study | Number of study subjects | Treatment mode                                                                 | Duration of study | Method of assessment | Results                                                                 | Adverse effects                                                                 |
|----------------------------|---------------|--------------------------|-------------------------------------------------------------------------------|-------------------|----------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Arellano et al., 2012[33]  | R, DB, SF, MC | 320 patients (308 completed initial phase and 242 maintenance phase) | Skin type III and IV<br>Daily application of TCC (FA 0.01% + HQ 4% + RA 0.05%) f/b<br>either of two maintenance regimens: twice weekly vs tapering regimen - 1st month, 2 week - 2nd month, 1 week - 4th month | Daily 8 weeks f/b 6 months maintenance | Primary efficacy - median time to relapse based on GSS<br>Secondary efficacy variable-GSS, MASI, Subject’s assessment | 78.8% subjects had no or mild melasma at week 8 and entered maintenance phase<br>53% of patients remained relapse-free in both groups<br>Twice weekly regime better than tapering regimen in postponing relapse in severe melasma | 11.6% AE<br>0.83% discontinued treatment due to AE<br>MC: Skin irritation and erythema<br>Telangiectasia was minimum |
| Grimes et al., 2010[34]    | O, Cohort     | 12 weeks of initial therapy f/b 12 weeks maintenance phase | TCC (HQ 4% + RA 0.05% + FA 0.01%)<br>Daily once at night for first 12 weeks<br>Next 12 weeks: Twice weekly application in clear to near clear patient<br>Daily treatment in those patients who did not attain clear state | 70 (52 completed) | Mexameter, MASI | Significant reduction in all the parameters of efficacy assessment<br>Telangiectasia was increased in the group receiving continuous therapy<br>53% patients reported one or more of AE<br>None discontinued | |
| Torok et al., 2005[35]     | R, B, MC      | 569 patients (389 and 327 completed 6 and 12 months) | TCC (FA 0.01% + HQ 4% + RA+0.05%)<br>Daily application in those patients who did not attain clear state | 12 months | Global assessment | >80% of patients had clear or near clear lesions<br>Most common - erythema (33%) and desquamation (29%)<br>Skin atrophy<1% Telangiectasia<4% | |

SF: Split face, O: Open, B: Blind, R: Randomized, MC: Multicentre, TCC: Triple combination cream, HQ: Hydroquinone, RA: Retinoic acid, FA: Flucinolone acetonide, MASI: Melasma Area and Severity Index, AE: Adverse effect, GSS: Global severity score
when used daily is invariably associated with AEs such as atrophy and telangiectasia. Although, the incidence was found to be low in the mentioned studies. It can be used as maintenance regimen for long-term response and is useful in preventing relapse. However, the frequency of application (daily/intermittent/tapering) determines the safety profile.

There is a paucity of well-designed RCTs evaluating the safety and efficacy of this regimen as maintenance therapy and duration of treatment in Indian population. Mometasone based TCC leads to the rapid lightening of pigmentation (within 3 weeks), but the relapse is also very fast. Further worsening of pigmentation and increase in the area of the original lesion has also been experienced by both the patients and physicians. Long-term use is invariably associated with topical steroid associated AEs such as atrophy, telangiectasia, hirsutism, and acneiform eruption.

**Table 6: Level and quality of evidence for melasma therapies using hydroquinone alone and in various combinations**

| Therapy | Level of evidence | Quality of evidence |
|---------|-------------------|---------------------|
| 2% HQ   | II                | C                   |
| 4% HQ   | I                 | B                   |
| 5% HQ1 0.1%-0.4% RA1 7% lactic acid/10% ascorbic acid | III | C |
| 3% HQ0.1% RA | III | C |
| 4% HQ0.05% RA+0.01% FA | I | A |
| 2% HQ1 0.05% RA1 0.1% dexamethasone (modified kligman) | III | C |
| 5% HQ, 0.1% RA, and 1% hydrocortisone | III | C |
| 2% HQ1 0.05% RA1 0.1% dexamethasone (modified kligman) | III | B |
| 1:30%-40% GA peel | II | B |
| 4% HQ+5% GA | II | C |
| 2% KA+2% HQ1 10% GA | II | C |
| 2% HQ+10% GA | II | C |
| 4% HQ+20/30% GA | I | B |

HQ: Hydroquinone, FA: Flucinolone acetonide, RA: Retinoic acid, GA: Glycolic acid, KA: Kojic acid

Due to the paucity of literature, we cannot make a recommendation for mequinol in melasma.

**Nonphenolic compounds**

**Corticosteroids**

Corticosteroids reduce pigmentation by decreasing the epidermal turnover and its anti-metabolic effect on melanocytes. Both fluorinated and nonfluorinated steroids have been used in the TCC in various formulations. However, their use as monotherapy is not recommended due to the plethora of AE and misuse by the patients.

**Azelaic acid**

Azelaic acid (AA) is a nonphenolic dicarboxylic acid that acts by competitively inhibiting tyrosinase enzyme. It inhibits DNA synthesis and mitochondrial enzymes causing anti-proliferative and cytotoxic effects on abnormal melanocytes. It has no effect on the normally pigmented skin.

In a prospective, single-blinded, split face comparison study, 40 Indian patients with melasma applied AA cream 20% to one half of the face for 24 weeks and clobetasol 0.05% for eight weeks followed by AzA cream 20% for the next 16 weeks. Sequential therapy was associated with more significant improvement than monotherapy.[40] AA has a good safety profile but may rarely cause erythema and stinging. By its efficacy and good safety profile, it is a good option for patients who cannot tolerate TCC. Table 7 summarizes the clinical trials with AA.[13,14,41-43]

**Level and quality of evidence: IB**

**Kojic acid**

Kojic acid (KA) is hydrophilic fungal derivative that inhibits tyrosinase, by chelating copper at the active site of the enzyme. It is used in a concentration of 1%-4%.

Various studies have been done to evaluate its role in melasma and these have shown mixed results [Table 8].[12,44-46] KA is less effective when used as monotherapy but shows good results in combination with HQ and GA.

**Level and quality of evidence: B**

**Arbutin**

It is a derivative of D-glucopyranoside that competitively inhibits tyrosinase and is cytotoxic to melanocytes. Deoxyarbutin is the synthetic derivative of arbutin with higher efficacy and stability. In a prospective, open-label study, a formulation containing nicotinamide 4%, arbutin 3%, bisabolol 1%, and retinaldehyde 0.05% was found to be associated with significant reduction in MASI scores.[47] Arbutin has also been used in combination with NdYAG laser and found to have good results in melasma.[48]
Sarkar, et al.: Medical management of Melasma-Indian Consensus Recommendations

Table 7: Summary of clinical trials with azelaic acid

| Reference          | Study type          | Patients | Treatment given                                                                 | Method of assessment | Results                                                                 | Side effects                                                                 |
|--------------------|---------------------|----------|----------------------------------------------------------------------------------|----------------------|------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Farshi[13]         | 29                  | 15: 4% HQ + SC 14: AA twice daily + SC for 2 months | MASI                 | Both groups showed significant improvement. AA group showed significantly greater reduction in MASI |
| Baliña and Graupe[14] | DB                  | 329 females | 4% HQ 20% AA | AA yielded 65% good or excellent results | Severe AE such as allergic sensitization or exogenous ochronosis were not observed with AA |
| Bansal et al.[41]  | 60 Indian patients  | Group A: Low fluence 0.5-13/cm² weekly intervals Group B: Twice daily application of 20% AA Group C: Combination of both for 12 weeks | MASI | Significant improvement seen in all three groups. Group C > Group A (P<0.001) and Group B (P<0.001) | Group B: Only 1 (5%) patient had slight burning sensation. In combination group, 1 (5%) patient developed erythema and 1 (5%) suffered slight burning sensation |
| Mahajan et al.[42] | Prospective randomized study | 40 | TCC once at night versus B: GA/AA 20% cream combination for 3 months Each group with 20 patients each received a dermocosmetic product containing AA for 24 weeks | Digital photography, MASI, VAS | Significant difference from baseline in both the groups. However, no significant difference between the groups | 4 patients in Group A and 3 in Group B had irritation, dryness and photosensitivity |
| Mazurek K et al.[43] 2016 | Comparative study | 60 females | Mexometer, corneometer, reviscometer | All dermocosmetics containing AA significantly reduced pigmentation. Largest decrease in pigment observed in first 3 months. combination containing 20% AA and mandelic acid, phytic acid, 4 N-butyl resorcinol, and ferulic acid proved to be the most effective dermocosmetic III

TCC: Triple combination cream, HQ: Hydroquinone, AA: Azelaic acid, MASI: Melanin Area and Severity Index, AE: Adverse effect, DB: Double blind, VAS: Visual analog scale, SC: Sunscreen, QSNL: Q Switched Nd Yag Laser

Level and quality of evidence: C

Vitamin C

Vitamin C inhibits melanogenesis by acting as a reducing agent at various oxidative steps in melanin synthesis. However, stability is an issue with the Vitamin C preparations due to rapid oxidation. Magnesium ascorbic phosphate is a stable esterified derivative of Vitamin C.

In a split-face RCT, 16 women with melasma used 5% AA and 4% HQ on either side of the face for 16 weeks.[17] HQ showed significantly better results but more AE (93% vs. 62.5%), as compared to Vitamin C.

Level and quality of evidence IB

Niacinamide

It is the active amide of Vitamin B3 that reduces pigmentation by inhibiting the transfer of melanosomes to keratinocytes. In a double-blind RCT, 4% niacinamide cream was compared with 4% HQ in 27 melasma patients. About 44% of patients showed good to excellent improvement with niacinamide compared to 55% with HQ. AE was less with niacinamide and histopathology showed decreased inflammatory infiltrate and solar elastosis in the treated lesions.[19]
Table 8: Summary of studies outlining the role of kojic acid in melasma

| Reference            | Study type | Patients | Treatment given | Duration | Method of assessment | Results | Adverse effects |
|----------------------|------------|----------|----------------|----------|----------------------|---------|-----------------|
| Deo et al., 2013     | SB, RCT    | 80 patients | Indian | Comparison in 4 groups | 12 weeks | MASI | Efficacy of Group B highest B > D > A > C |
| Deo et al., 2013     | SB, RCT    | 80 patients | Indian | Group A: KA 1% | 12 weeks | MASI | Efficacy of Group B highest B > D > A > C |
| Deo et al., 2013     | SB, RCT    | 80 patients | Indian | Group B: KA 1% + HQ 2% | 12 weeks | MASI | Efficacy of Group B highest B > D > A > C |
| Deo et al., 2013     | SB, RCT    | 80 patients | Indian | Group C: KA 1% + BV 0.1% | 12 weeks | MASI | Efficacy of Group B highest B > D > A > C |
| Deo et al., 2013     | SB, RCT    | 80 patients | Indian | Group D: KA 1% + HQ 2% + BV 0.1% | 12 weeks | MASI | Efficacy of Group B highest B > D > A > C |
| Monteiro et al., 2013| DB, RCT    | 60       | 4% HQ versus 0.75% KA + 2.5% Vitamin C | 12 weeks | MASI | HQ cream superior to KA |
| Lim, 1999            | DB, SF, RCT| 40 Chinese women | 2% KA + 10% GA + 2% HQ versus 10% GA + 2% HQ | 12 weeks | Clinical evaluation | Side receiving KA did better (60% versus 47% improvement) |
| Lim, 1999            | DB, SF, RCT| 40 Chinese women | 2% KA + 10% GA + 2% HQ versus 10% GA + 2% HQ | 12 weeks | Clinical evaluation | Side receiving KA did better (60% versus 47% improvement) |
| Garcia and Fulton, 1996 | SF, RCT    | 39 patients | 5% GA+HQ 2% versus 5% GA + KA 2% | 3 months | Subjective, wood’s light | 51% responded. Equal efficacy of KA and HQ |
| Garcia and Fulton, 1996 | SF, RCT    | 39 patients | 5% GA+HQ 2% versus 5% GA + KA 2% | 3 months | Subjective, wood’s light | 51% responded. Equal efficacy of KA and HQ |

SF: Split face, DB: Double-blind, SB: Single blind, RCT: Randomized controlled trial, HQ: Hydroquinone, KA: Kojic Acid, BV: Betamethasone valerate, MASI: Melasma Area and Severity Index

Level and quality of evidence: IB

Newer drugs

A number of newer derivatives of the conventional drugs, synthetic compounds and botanicals derived from natural sources are being studied for their potential role in reducing melanogenesis and pigmentation. These compounds have been found to lighten melasma and hyperpigmentation induced by UV exposure. They can prove to be effective in the treatment of melasma, especially as adjuncts to first-line treatments and for maintenance. These agents work through various mechanisms such as inhibition of activity or maturation of tyrosinase enzyme as well as acceleration of its degradation. Other mechanisms include anti-inflammatory, antioxidant, peroxidase inhibition or breaking down melanin, prevention of transfer of melanosomes from melanocytes to the keratinocytes (nicinamide) and stimulation of peroxisome proliferator-activated receptors (octadienedioic acid).

A number of these drugs have been studied in human trials on melasma, solar lentigines or UV induced hyperpigmentation with encouraging results as elucidated in Table 9. Others such as cinnamic acid, green tea extracts, flavonoids, gentistic acid, pyronic acrylic acid inhibitors, zinc dihydroxyphystidinate and resveratrol are in the process of development. The knowledge of the properties of these agents enables the dermatologist to choose a product that gives the best benefit to their patients while minimizing the side effects. Although experimental evidence suggests their possible benefits, rigorous controlled trials are mostly lacking for these agents. Thus, these cannot be strongly recommended for melasma at present and more studies are required to further elucidate their role.

Oral drugs for melasma

Tranexamic acid (TXA) (Trans-4-Aminomethylcyclohexane-carboxylic acid) is a synthetic derivative of the amino acid lysine. It binds reversibly to the lysine binding sites on plasminogen molecules and inhibits plasminogen activator (PA) and thus the conversion of plasminogen to plasmin. Plasminogen also exists in the basal epidermal cells and keratinocytes and induction of this keratinocyte-PA system by UV exposure results in melanogenesis through production of prostaglandins and leukotrienes. It is through prevention of binding of plasminogen to keratinocyte, TA inhibits UV-induced plasmin activity in keratinocytes, thereby decreasing melanogenesis through reduced production of PGs.

The effect of oral TA in melasma has been studied in multiple trials, as summarized in Table 10. However, only two of them are RCTs. Padhi and Pradhan evaluated the efficacy of oral TA in 40 Indian patients who were given oral TXA (250 mg twice a day for 8 weeks) in addition to a TCC, (fluocinolone acetonide 0.01%, tretinoin 0.05%, and HQ2%). There was a faster reduction in MASI in the combination group and the efficacy was maintained throughout the 6 months follow-up period.

In another RCT conducted by Karn et al., in 260 patients of melasma, the efficacy of TA was
| Drug                | Derived from          | Mechanism                                      | References | Type                | Treatment model                                                                 | Treatment duration | Number of patients | Result                                      | Side effect | Level of evidence | Quality of evidence |
|---------------------|-----------------------|------------------------------------------------|------------|---------------------|--------------------------------------------------------------------------------|-------------------|-------------------|---------------------------------------------|-------------|-------------------|---------------------|
| 4 Hydroxyanisol     | Derivative of HQ      | Inhibition of tyrosinase                        | Keeling *et al.*, 2008[39]                 | Case series | Mequinol 2%/tretinoin 0.01% topical solution                                | Treatment duration - 12 weeks Follow up - upto 16 week  | 5 men with melasma    | Complete clearance of melasma at 12 weeks in 4/5 patients. Results maintained at the 16-week follow-up visit | Minimal adverse effects | II–III             | C                   |
| Lignin peroxidase   | Fungus *phanerochaete* | oxidizing and breaking down melanin            | Mauricio *et al.*, 2011[49]               | Double-blind, SF RCT | LP versus 2% HQ cream or placebo on either side of face                    | 31 days            | 51 Asian patients | LP cream provided significant skin-lightening as compared to HQ Rapid effect, seen as early as 7 days | Minimal adverse effects | I                 | B                   |
|                     | *chrysosporium*       |                                                 |            |                     |                                                                                |                   |                   | Parity between LP and HQ in skin lightening, whereas, LP superior to the placebo |                   |                   |                     |
|                     |                       |                                                 |            |                     |                                                                                |                   |                   | LP superior in skin texture and roughness as compared to HQ |                   |                   |                     |
| Magnolignan         | Biphenyl compound     | inhibits the maturation of tyrosinase          | Takeda *et al.*, 2006[51]                 | Cohort study | 0.5% Magnolignan® topical application to pigmented areas on the face       | 6 months           | 51 female patients with melasma, senile lentigo, etc. | Significant improvement of the melasma Lightening of nonpigmented healthy skin also seen | No unfavorable skin reaction | II–II              | C                   |

*Contd...*
### Table 9: Contd...

| Drug          | Derived from | Mechanism                                                                 | References                          | Type                  | Treatment model                                                                 | Treatment duration | Number of patients | Result                                                                                                                                   | Side effect                                                                 | Level of evidence | Quality of evidence |
|---------------|--------------|---------------------------------------------------------------------------|-------------------------------------|-----------------------|---------------------------------------------------------------------------------|--------------------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|------------------|---------------------|
| NAG           | Monomeric unit of chitin inhibiting the conversion of protyrosinase to tyrosinase | Iraji et al., 2009[52]            | Double-blind, split-face RCT       | Combination of 4% NAG and 2% nicotinamide versus 4% HQ on each side of face | 12 weeks            | 30 females (aged 20-50 years) | Although statistically nonsignificant, efficacy of NAG+nicotinamide slightly more than HQ Side effects of NAG+nicotinamide slightly less than HQ | Minimal adverse effects | I                | B                   |
| Orchid extracts | Contains flavanoids antioxidant | Tadokoro et al., 2010[53] | O, SF study                         | Plant extracts including orchid extracts versus 3% Vitamin C derivative | 8 weeks              | 48 Japanese females (30-60 years) With melasma and/or lentigo senilis | Significant improvement with plant extracts (orchid extracts) formulation, parity with Vitamin C | Minimal adverse effects | II–II             | C                   |
| Dioic acid    | Biofermentation of oleic acid affects tyrosinase transcription and melanosome transfer | Tirado-Sanchez et al., 2009[54] | 0, comparative study               | 1% dioic acid versus 2% HQ | 12 weeks                          | 96 Mexican female patients | Significant reduction in pigmentation, parity with HQ | Lesser side effects than HQ | II–II             | C                   |
| Octadienedioic acid | Structural similarity to AA Stimulation of PPARs, modulatesynthesis of tyrosinase mRNA | Wiechers et al.[55] | Comparative study                  | 1% ODA versus 2% arbutin, were both applied on either forearm | Treatment duration - 8 weeks Follow up - 4 weeks | 21 Chinese volunteers | Mild to moderate benefit in skin lightening | Minimal adverse effects | II–II             | C                   |
| B-Carotene    | Structural analog of Vitamin A saturates melanocyte receptors and reduce melanin production | Kar, 2002[56] | Open study                          | B-carotene lotion on melasma | 8 weeks                          | 31 adults (26 female and 5 male) | Moderate benefit in melasma | Minimal adverse effects | II–II             | C                   |

Contd...
| Drug          | Derived from          | Mechanism                      | References | Type       | Treatment model                                                                 | Treatment duration | Number of patients | Result                                                                 | Side effect | Level of evidence | Quality of evidence |
|--------------|-----------------------|--------------------------------|------------|------------|--------------------------------------------------------------------------------|---------------------|-------------------|----------------------------------------------------------------------|-------------|-------------------|---------------------|
| Linoleic acid| Derived from hydroxylated botanical oils e.g., safflower | Accelerate tyrosinase degradation | Lee et al., 2002[57] | Double-blind RCT | 2% LM with 0.05% BV versus 2% LM with 0.05% BV and 2% LA versus vehicle Divided into 3 groups of 20 each, vehicle (Group A), 2% LM mixed with 0.05% BV (Group B), or 2% LM mixed with 0.05% BV and 2% LA (Group C) on the face every night | 6 weeks           | 60                | 2% LM mixed with 0.05% BM and 2% LA caused significant improvement in melasma as compared to vehicle or LM with BA | Minimal adverse effects | I                 | B                   |
| Silymarin    | Plant Silybum marinum | Inhibits melanogenesis          | Elfar and El-Maghraby, 2015[58] | Comparative study | TXA injection versus silymarin versus 50% GA peels Divided into 3 groups of 20 patients each: group A (intradermal TXA injection), Group B (topical silymarin cream) and group C (GA peeling 50%) | 60 female patients | Topical silymarin showed moderate benefit in melasma, parity with GA peel, superior to intradermal TXA | Minimal adverse effects | II–II            | C                   |
| 5% methimazole | Oral antithyroid drug | Peroxidase inhibitor            | Malek et al., 2013[59] | Case report | 5% methimazole on melasma | 8 weeks | Two HQ-resistant melasma patients | Significant improvement of melanoma | Minimal adverse effects | III               | C                   |
| Pidobenzone  | Phenolic compound     |                                 | Zanieri et al.[60] | Case series | 4% pidobenzone gel | 16 weeks | Significant benefit in melanoma | Minimal adverse effects | II–III           | C                   |
| Drug                      | Derived from | Mechanism                   | References       | Type                      | Treatment model | Treatment duration | Number of patients | Result                                                                 | Side effect                                                                 | Level of evidence | Quality of evidence |
|--------------------------|--------------|-----------------------------|------------------|---------------------------|-----------------|-------------------|-------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------|------------------|---------------------|
| Rucinol                  | 4-n-butylresorcinol | Inhibition of tyrosinase and TRP-1 | Khemis et al., 2007[61] | Double-blind, split-face RCT | 0.3% rucinol versus vehicle | 12 weeks     | 32 patients         | Lower pigmentation score on the rucinol-treated side benefits were maintained for another 12 weeks | Mild stinging, burning, erythema, peeling, dryness, desquamation            | I                | B                   |
|                         |              |                             | Huh et al., 2010[62] | Double-blind, split-face RCT | 0.1% liposome-encapsulated rucinol versus vehicle | 8 weeks       | 23 patients         | Significantly lower pigmentation scores with the liposome encapsulated rucinol | No adverse effects reported                                                   |                  |                     |
| Licorice extract         | Glycyrrhiza glabra, glabridin | Tyrosinase inhibition and anti-inflammatory | Costa et al., 2010[63] | Mono-blind RCT | Emblica, licorice, and belides 7% versus 2% HQ | 60 days       | 56 patients         | Moderate improvement in melasma. Rity between both groups               | Side effects like burning and increase of the number of previous acne lesions in 2 patients; but lesser than those with HQ | I                | B                   |
| N-Acetyl-4-S-cysteaminyphenol | Phenolic agent | Tyrosinase inhibition | Jimbow, 1991[64] | Case series | N-acetyl-4-S-cysteaminyphenol on melasma | 6 months      | 12 patients         | Significant benefit in melasma                                          | Recurrence of pigmentation in a patient after withdrawal of drug Acneiform eruptions in one patient | II–III           | C                   |

Contd...
compared to routine topical treatment. One group received oral TA 250 mg twice a day for 3 months along with routine topical measures, whereas the other group received routine topical treatment alone.\textsuperscript{67} The combination treatment group showed statistically significant decrease in mean MASI from baseline to 8 and 12 weeks. The authors concluded that oral TA provides rapid and sustained improvement in the treatment of melasma.

Overall recommendation: as per available evidence, oral TA may be used alone or as an adjuvant to conventional topical drugs. It can also be used when other topical treatments fail. However, there are limited studies with small sample size and variable dosage and duration. Larger RCTs are required to evaluate the efficacy and long-term follow-up as well as serious AE.

**Other oral drugs**

**Procyanidin**

There is only one RCT that has evaluated the efficacy of oral procyanidin in melasma. In this double-blind, placebo-controlled trial conducted by Handog EB \textit{et al.}, in 60 Filipino women with epidermal melasma, the safety and efficacy of oral procyanidin plus Vitamin A, C, E were compared with placebo.\textsuperscript{75} The patients received either the drug or placebo twice daily with meals for 8 weeks. Results were evaluated using mexameter, MASI and global evaluation by the patient. The procyanidin group showed a significant improvement in pigmentation with minimal AEs.

However, this study had the limitation that procyanidin was not evaluated as monotherapy and thus, the benefit achieved cannot be ascribed to procyanidin alone.

**Evidence level-B**

**Oral polypodium leucotomos extract**

One double-blinded RCT was done with oral polypodium leucotomos extract (240-mg thrice a day) for 12 weeks among 40 hispanic patients with moderate to severe melasma.\textsuperscript{76} There was an improvement in MASI and melasma-related quality-of-life, but it was not statistically significant.

**Evidence level B**

Recommendation: there is lack of evidence to recommend this drug in melisma.

**Pycnogenol**

Pycnogenol is an extract of the bark of Pinus pinaster, a French pine tree. It has antioxidant properties, increases the endogenous antioxidant enzyme system and also protects against UV radiation. Its efficacy in melasma was evaluated in a single clinical trial conducted by Ni \textit{et al.} in 30 women with melasma who took one tablet of Pycnogenol (25 mg) with meals three times daily for 30 days.\textsuperscript{77} MASI and pigmented intensity index
### Table 10: Summary of clinical trials with tranexamic acid

| References          | Study type  | Patients                                         | Treatment given                                    | Duration | Method of assessment                  | Results                                      | Adverse effect |
|---------------------|-------------|--------------------------------------------------|---------------------------------------------------|----------|---------------------------------------|----------------------------------------------|---------------|
| Lee et al., 2016    | Retrospective analysis | 561 Asian patients | Oral TA                                           | 4 months | MASI, PGA                             | 89.7% improved 10% no improvement             | AE in 7.1% Relapse rate 27.2% |
| Tan et al., 2016    | Retrospective analysis | 25 patients, mixed race Melasma refractory to topical agents | Oral TA 250 mg BD+pre-existing combination topical treatment (not specified) | Mean period of treatment: 3.7 ± 0.33 months Follow up: 6 months | MASI, PGA                             | Mean improvement: 69% at 3 months 72% had relapse of melasma within 2 months of stopping TA despite continuance of topical agents |
| Padhi and Pradhan, 2015 | O, RCT | 40 Indian patients (20 each group) | Group A: TCC only Group B: Oral TA 250 mg BD + TCC | 8 weeks Follow up - 6 months | MASI | Group A: significant and faster improvement, maintained for 6 months |
| Na et al., 2013     | 0, NR, uncontrolled | 25 Korean females | Oral TA 250 mg TDS | 8 weeks | Mexameter, histopathology and IHC (CD31 Ab, anti-tryptase Ab) | MI and erythema index decreased significantly Histology: Reduction of epidermal pigmentation, vessel no and mast cell counts Score decreased significantly in both groups, better response in combination group |
| Shin et al., 2013   | RCT | 48 Korean female patients | Group 1: Laser-oral TA Group 2: Laser (2 sessions of low fluence Q-switched NdYAG laser) | 8 weeks | Modified MASI, clinical improvement scale | Statistically significant decrease in mean MASI from baseline to 8 and 12 weeks in Group A |
| Karn et al., 2012   | RCT | 260 Nepalese patients (130 in each group) | Group A: 130 patients, HQ + oral TA 250 mg BD Group B: HQ | 3 months | MASI | Statistically significant decrease in mean MASI from baseline to 8 and 12 weeks in Group A |
| Cho et al., 2013    | Retrospective analysis | 51 Korean females | Group A: Oral TA + IPL + laser (Q-switched NdYAG) Group B: IPL + Laser | 4 months | MASI | Significantly better response in Group A |

Contd...
decreased after treatment. Several other symptoms such as fatigue, constipation, pains in the body, and anxiety were also improved, and no AE was seen.

It cannot be recommended in melasma until further studies are available.

**Glutathione**

No available study in melasma

### Conclusions

Medical management of melasma with topical skin lightening therapy still remains the mainstay of therapy and should always be used as first-line agents. HQ, triple combination therapy, other agents and upcoming oral therapies will be used in combination in the future. The SPF with the Pigmentary Disorders Society suggests an easy to follow an algorithm, Figure 1,
where peels and lasers form second- and third-line therapies respectively.

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**Conflicts of interest**

There are no conflicts of interest.

### What is new?

- Although topical therapy with hydroquinone and triple combination therapy leads the list in treatment of melasma, a careful watch for side effects of topical corticosteroids must be done. Mometasone or fluticasone containing creams should be totally discouraged.
- A large number of newer botanical agents offer a suitable alternative and should be used for maintaining lightening of melasma.
- Sunscreens containing more of inorganic sunscreens especially iron oxide appear more promising.
- Oral agents, especially tranexamic acid has been well studied and used but does need more follow up for side effects.
- Treatment of medical conditions concomitantly is important.

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