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REVIEW

Evidence-Based Treatment for Melasma: Expert Opinion and a Review

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ABSTRACT

Introduction: Melasma is one of the most common pigmentary disorders seen by dermatologists and often occurs among women with darker complexion (Fitzpatrick skin type IV–VI). Even though melasma is a widely recognized cause of significant cosmetic disfigurement worldwide and in India, there is a lack of systematic and clinically usable treatment algorithms and guidelines for melasma management. The present article outlines the epidemiology of melasma, reviews the various treatment options along with their mode of action, underscores the diagnostic dilemmas and quantification of illness, and weighs the evidence of currently available therapies.

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Methods: A panel of eminent dermatologists was created and their expert opinion was sought to address lacunae in information to arrive at a working algorithm for optimizing outcome in Indian patients. A thorough literature search from recognized medical databases preceded the panel discussions. The discussions and consensus from

melasma management, including clinical assessment, investigations, drug therapies, combinations, procedural therapies, and newer emerging therapies, from peer reviewed journals were included. Articles not adequately powered or not randomized with poorly defined methodology and articles with conflicting or non-committal results were excluded.

A total of 115 publications until August 2013 were obtained by electronic database searches of which 52 were randomized controlled trials (1 retrospective) and 42 were review articles (17 were reviews and discussions of specific drug/ combination or procedural treatment). The remaining publications included eight articles on prevalence data, five articles of case series, five articles on investigations and histopathology, and three articles on validating scoring and grading systems. The literature search was completed and then followed by three panel discussion sessions, each in the form of a 1-day residential focused program where clinical experiences of each panelist were brought to the table along with the study of the associated literature and publications. All discussions, suggestions, and panel consensus were recorded by a medical writer who was present. In addition, experienced persons from the field of pharmaceuticals also contributed with respect to the pharmacological aspects of the various drug therapies. In between each of these sessions, the outcome and consensus of the previous session were drafted and shared with the panel members for further refining. After all panel discussion sessions were concluded, the final draft of the panel consensus and algorithm was prepared along with the summary of the reviewed literature. This draft was finally refined and accepted by the panelists to come up with a clinically practical, relevant, and acceptable treatment algorithm for melasma. The deployment of this algorithm is expected to act as a basis for guiding and refining therapy in the future.

This article is based on previously conducted studies and the expert opinion of the authors, and does not involve any new studies of human or animal subjects performed by any of the

depigmentation. Pigment reduction is achieved by using chemicals that interfere with various steps of the melanogenesis pathways via: (i) the retardation of proliferations of melanocytes; (ii) the inhibition of melanosome formation and melanin synthesis; and (iii) the enhancement of melanosome degradation [15]. Table 1 shows the classification of the pigment-reducing agents based on their mechanism of action [16–18].

First-line therapy usually consists of topical compounds that affect the melanin synthesis pathway, broad-spectrum photoprotection, and camouflage. Chemical peels are often added in second-line therapy. Laser and light therapies represent potentially promising options for patients who are refractory to other modalities, but also carry a significant risk of worsening the disease. A thorough understanding of the risks and benefits of various therapeutic options is crucial in selecting the best treatment.

T 1 C a ca p a a c a ac [16 18]

S	**D**	**A**
B a	T a a c p	T , c-2 c a
	T a c a	$PaSSO_3Ca$
	I b p a	T a a c ac
D a	T a b	H , , a a c ac , c ac , a b , a b , c c ac , c , 2,5- -4- -3(2H)- a , *N*- ac c a , a , a , a c ac , a , 4- a
	P a b	P c c p
	R ac p c ca	A c b c ac , a c b c ac pa a , c ac , c a
A a	T a a a	L c ac , α- c ac
	I b a	N ac a , p a b , , c , a cp , b a p b
	S acc a	Lac c ac , c c ac , c ac , c ac
	R a a c	C c , ab
	I ac c pp	K c ac , a c b c ac
	I b a a a	A b a a b
	I b p a ac a cp 2	S b a p b

CLINICAL ASSESSMENT OF MELASMA

Traditionally, Wood's lamp examination is done to identify the location of pigment, but is limited to epidermal melasma and cannot be used reliably in Fitzpatrick skin types V and VI as dark-skin melanin pigmentation obscures the detection of dermal melanin [19]. Melasma is reliably graded on the basis of area and severity parameters [i.e., melasma area and severity index (MASI) score] [20, 21].

PHARMACOLOGIC THERAPY

Sunscreens

Sunscreen use is vital throughout treatment and post-treatment to prevent hyperpigmentation and relapse of melasma. Broad-spectrum anti-UV A and B sunscreens with physical blocking agents like ZnO and TiO_2 (SPF >30) should be used regularly to cover the affected areas. Patients with Fitzpatrick IV to VI skin types [22] are at a heightened risk from sun exposure [23, 24]. Indian patients avoid sunscreens due to oily, sticky nature and heat from exothermic reaction of chemicals. However, physical sunscreens do not release heat.

Hydroquinone

Hydroquinone (HQ; dihydroxybenzene) is structurally similar to precursors of melanin. HQ inhibits the conversion of dopa to melanin by blocking tyrosinase action [25] and inhibits the formation, melanization, and degradation of melanosomes. HQ also affects the membranous structures of melanocytes and eventually causes necrosis of whole melanocytes [26].

HQ has been used to treat hyperpigmentation for more than 50 years. While controversy exists regarding the long-term safety of HQ, its efficacy in treating melasma, both alone and in combination with other agents is well established [5]. HQ 2–4% is prominently used as a mono-therapy or in a combination cream. HQ preparations >5% are not recommended due to irritation, except for refractory cases [27, 28]. Pigment lightening by HQ becomes evident after 5–7 weeks of the treatment. Treatment with HQ should be continued for at least 3 months and up to 1 year [29].

For patients on HQ therapy, regular medical follow-up is essential: every 3 months for high phototype skin (Fitzpatrick type V and VI) patients and every 6 months for lighter skin types. Common adverse events (AEs) are erythema and burning. Other rare AEs are ochronosis and confetti-like depigmentation. Speckling or reticulation indicates ochronosis. Histopathology shows short, stout, curvilinear, ochre-colored fibers in the papillary dermis [30].

Tretinoin

Tretinoin, a retinoid (RA), inhibits transcription of the key melanin synthesis enzyme tyrosinase [16–18]. Tretinoin plays an important role in the triple-combination cream (described later) and is used as a chemical peel.

Corticosteroids

Topical corticosteroids are anti-inflammatory molecules that exert an anti-metabolic effect on melanocytes, resulting in a decreased epidermal turnover and thus, may produce a mild pigment-reducing effect [31]. Corticosteroids are an active component of the triple-combination creams. Triple formulations

using different corticosteroids have shown efficacy, for example, dexamethasone [32], hydrocortisone 1% [33], mometasone [34, 35], and fluorinated steroids [22, 36–41]. Researchers found that fluorinated steroids were more effective and safer than non-fluorinated steroids, for example, 0.01% fluocinolone acetonide and fluticasone [22].

Kojic Acid

Kojic acid can substitute for HQ if a patient is intolerant to HQ. Kojic acid inhibits tyrosinase by chelating copper at the enzyme's active site. It is available in 1–4% concentrations, and also in combination with HQ. Caution is required in its use as kojic acid is a known sensitizer [5].

Azelaic Acid

Azelaic acid (AA) is anti-proliferative and selectively cytotoxic towards hyperactive melanocytes, inhibiting tyrosinase and mitochondrial oxidoreductase enzymes with minimal effects on normally pigmented skin [42]. In different trials, AA treatment was found to be less or as equally efficacious as HQ [42, 43] and hence may be used in case of intolerance to HQ.

Triple Combination

Based on the current evidence: sun avoidance, sunscreen use, and triple combination regimen is the most effective first-line treatment for melasma. Combination creams are more efficient bleaching agents than mono-therapies. The combination of HQ, a RA, and a topical steroid (5% HQ, 0.1% RA, and 0.1% dexamethasone), or Kligman and Willis' formula was developed to enhance the efficacy of each individual ingredient, shortening the duration of therapy and reducing the risk of AEs [44, 45]. Since then, some variation of this formula is the most commonly used therapy for melasma worldwide [32]. Tretinoin prevents the oxidation of HQ and improves epidermal penetration while the steroid reduces irritation from the other two ingredients and suppresses biosynthetic and secretory functions of melanocytes, leading to an early response in melasma. The synergistic action of the three topical agents achieves significantly higher depigmentation than either agent alone. Improvement is seen in 8 weeks without any significant AE [46].

In India, a cream-based combination of HQ, tretinoin and mometasone has been extensively used after its launch in 2004. Long-term use on the face (generally >12 weeks) of corticosteroids, particularly mid-potent ones like mometasone can cause skin atrophy, telangiectasias, and/or an acneiform eruption [37]. Moreover, a relapse is common when mometasone use is stopped [47]. The combination treatment is supposed to be used for a maximum of 4–8 weeks after which the treatment should be stopped or the dose gradually reduced, and finally replaced with safer treatment modalities [48]. We found mometasone-based combination with glycolic acid (GA) peels caused AEs like hyperpigmentation, irritation, and persistent erythema in 2 out of 10 patients (20%) [34]. Triple-combination creams with mometasone should be prescribed only after thorough patient counseling with explanation of long-term AEs.

Evidence-based studies have shown triple combination of 4% HQ with 0.05% tretinoin and 0.01% fluocinolone acetonide to be the most efficacious and safe available topical modality for the first-line treatment of melasma [40, 41]. It is the only ointment

currently approved by the US Food and Drug Administration for the treatment of melasma. The safety and efficacy of the combination was initially demonstrated in 641 melasma patients in a multicenter, investigator blinded, randomized prospective trial [36, 39–41]. Night use of the triple-combination cream as compared to dual-combination creams (HQ + tretinoin, HQ + fluocinolone, or tretinoin + fluocinolone) achieved complete or near-complete clearance in 77% of patients. Clinically significant improvement was noted within 4–8 weeks [39]. The most common AEs were mild local irritation, erythema, and skin peeling. For the Indian skin, which is mostly of Fitzpatrick type IV–VI, a reduced HQ combination of 2% HQ + 0.05% tretinoin + 0.01% fluocinolone acetonide (HQ + RA + FA) was launched in 2010 [47]. Safety studies in Indian population need to be established. A recent Cochrane review of 20 studies with a total of 2,125 participants with 23 different treatments concluded that triple-combination cream was significantly more effective than HQ alone (relative risk 1.58, 95% CI 1.26–1.97) or dual combination [38].

The fluocinolone-based triple cream is safe in the treatment of moderate to severe melasma for up to 24 weeks. The risk of skin atrophy after 6 months of treatment with fluocinolone acetonide 0.01%, HQ 4%, and tretinoin 0.05% cream is very low as shown by histological examination [4].

In the expert opinion of the authors, fluticasone seems more effective and safer than mometasone and fluocinolone in the triple combination due to less long-term (> 12 weeks) steroidal AEs. Once-daily application of fluticasone (0.05%) was as efficacious as twice-daily application of betamethasone (0.12%), with less skin atrophy and an absence of systemic AE of hypothalamic–pituitary–adrenal axis suppression [37]. In another study, fluticasone did not cause cortisol suppression or major skin atophy, and was similar to mometasone furoate in efficacy [49].

Dual Combination

The dual combinations are recommended if triple combination is not available or if patients are intolerant to it. Those available in India include HQ and GA, HQ and Kojic acid, and mequinol and tretinoin. Table 2 gives an overview of studies that provide evidence on topical agents for treating melasma.

Adjunctive Therapies

These include a wide range of chemicals and natural extracts have been tested against melasma (Table 3). Tranexamic acid is the most common adjunctive therapy to be used and works by decreasing melanogenesis in epidermal melanocytes and provides a rapid and sustained lightening in melasma [50–53]. Other therapies include a substance called ‘antipollon’, a finely grained aluminum silicate that possesses the ability to adsorb melanin. Laboratory studies with different concentrations have shown up to 86% melanin adsorption with 0.8% antipollon. However, clinical studies establishing its efficacy are awaited (Antipollon-HT efficacy testing Nikkol Chemicals, data on file).

Interventions

Intervention procedures are used in combination with topical first-line therapy to treat recalcitrant melasma when patient shows poor or no response. Intervention techniques include chemical peels, lasers, intense pulsed

T 2 E c p a p ca a p

R	S h>	T	P ,	S	T	R
M a. [77]	R, DB	4% HQ . ac b + SPF 30	48	N/K	20	38% HQ/8.3% ac b , a p
Ha a [27]	R, DB, SF	4% HQ . ac b + SPF 25	30	N/K	3	79% HQ/67% SWC p
Fa [78]	R, O	4% HQ . a ac ac 20%	29	N/K	2	A 2 a , MASI c a 6.2 ± 3.6 HQ a 3.8 ± 2.8 a ac ac
E p a-P a. [79]	R, O, SF	4% HQ . 5% a c b c ac	16	N/K	16	HQ 93% a c , c pa 62.5% a c b c ac . S c p 68.7% HQ . 6.2% a c b c ac
Na a a. [80]	R, O	P 2% HQ . 0.025% RA c a ( ) 2 b a. c ac c ac p (2 12)	50	N/K	6	HQ p RA a ap a a ac p a c a c c p p ac p p a
Ba a a G a p [43]	R, DB, MC	4% HQ . 20% a ac ac	329	N/K	24	65%/73% c a ac/HQ pa
P Ma a. [81], V a - R a. [82]	R, DB O	4% HQ . 20% a ac ac	60	N/K	24	A ac ac a b a HQ a a a
V a -R a. [82], L [83]	R, DB	2% HQ . 20% a ac ac	155	N/K	24	73% a ac ac pa , c pa 19% HQ pa , a c a
L [83], F a C a. [84]	R	2% KA, 2% HQ, 10% GA . 2% HQ, 10% GA	40	N/K	12	2% KA, 2% HQ, 10% GA p 60% . 47.5% 2% HQ, 10% GA
F a C a a. [84], G a. [85]	R, O	4% HQ, 0.05% RA, 0.01% FA (TC) . 4% HQ + SPF 30	120	M/S	8	>75% p , 73% TC/49% HQ ($P = 0.007$)
Ta a. [39]	R, SB	4% HQ, 0.05% RA, 0.01% FA (TC) . 4% HQ, 0.05% RA 0.05% RA, 0.01% FA 4% HQ, 0.01% FA + SPF 3	641	M/S	8	77% TC; 47% HQ/RA; 27% FA/RA; 42% HQ/ FA, c a /a c a
T [41]	R, O, MC	4% HQ, 0.05% RA, 0.01% FA (TC) + SPF 30	585	M/S	12	B 12: 80% c a a c a b p c a a (pa a)
G a. [85]	MC, O	4% HQ, 0.05% RA, 0.01% FA (TC) + SPF 30	1,290	M/S	8	75% c a a c a a 8 b p c a a
W a. [50]	O	TA 250 b	74	N/K	6	E c (10.8%, 8/74), (54%, 40/74), a (31.1%, 23/74), a p (4.1%, 3/74). S c TA c a a a c (5.4%) a p a (8.1%) b . R c c a a a b ca (9.5%)
Ka c Na A a a a. [51]	R, DB, O, SF	T p ca TA 5% . ac b	23	N/K	12	R ca b
L a. [52]	O	0.05 L TA (4 / L) a c a a	100	N/K	12	(9.4%) a a (51 75%), 65 pa (76.5%) a a (26 50%), a 12 pa (14.1%) a p (0 25%)

DB b b , *FA* c ac a , *GA* c c ac , *HQ* , *KA* c ac , *MASI* M a a A a S I , *M/S* a / , *MC* c , *N/K* , *O* p , *R* a , *RA* , *SB* b , *SF* p ac , *SPF* p c ac , *SWC* c a , *TC* p c b a , *TA* a a c ac

T 3 A c a p c a a a [86]

T	
T a a c ac	
V a C	
V a E	
S b a ac	
T p ca	
L c c ac	
G a	
B a b ac	
P p b ac	
A b	
I ac	
N ac a	
N c c ac	
4-*N* b c c	
M a	

light (IPL), cryosurgery, dermabrasion, and micro-dermabrasion. They are not considered as first-line therapy as they can cause PIH and are often ineffective [54–56]. Chemical peels, lasers, and IPL are described here as their use in melasma is better studied in the Indian setting to some extent.

Chemical Peels

Chemical peels used for treating melasma are described in Table 4. There is a medium-quality evidence to suggest that undergoing serial chemical peels with GA, salicylic acid, or trichloroacetic acid (TCA) is moderately effective in the treatment of melasma (Table 5) [22, 53, 57, 58]. GA peels are used as an adjunctive therapy in refractory cases of epidermal melasma as they enhance the efficacy of topical regimen [59]. There are many studies comparing GA and other peels for melasma in dark-skinned patients (Table 6) [53].

Chemical peels cause controlled exfoliation, followed by regeneration of epidermis and dermis [60]. Superficial and medium-depth peels have been employed with variable success in the treatment of melasma. After a superficial peel, epidermal regeneration can be expected within 3–5 days and desquamation is usually well accepted [61]. Because of the risk of prolonged dyschromia, medium-depth and deep peels should be avoided in patients with dark skin. In the authors' opinion, maintenance sessions or repeat sessions may be necessary. Patients should be well informed.

Lasers and Light Therapy

Lasers have a limited role in the treatment of melasma. Though successful use of Q-switched (QS) lasers [50], fractional lasers [57, 62–66], IPL [56], and combination lasers [67–69] has been reported, response to treatment is unpredictable and pigmentation frequently recurs. In addition, PIH is common in Indian patients. Hence, a maintenance schedule has to be initiated and continued. For these reasons, lasers are not routinely recommended as the treatment of choice for melasma in Indian patients. It may be used in selected resistant cases, at the discretion of the treating physician, after proper counseling. A test patch may be performed prior to treating the lesion. QS laser and low-fluence mode laser toning alone or in combination with either fractional CO_2 laser or IPL have shown reasonable success in treating melasma of Asian patients (Table 7). A number of studies have shown successful treatment of melasma with fractional lasers [non-ablative Er (Erbium): Glass 1,540/1,550 nm lasers], and they are recommended in all skin types [57, 62–65].

T 4 T a a c ca p

C	T	C
GA	30 70%. S p ca p . A a p , a GA p a app 3 5 2 3 . T p a a 1% b ca b a [53, 56, 58 60, 73, 87, 88]	
LA	92%. S p ca p . 2 c a LA a pH 3.5 a app 10 3 [87 89]	Sa a c , ac
SA	S p ca p . 20 30% p HQ a 2- a	T c a c a, p ca p b ca [62]. A a SA a a a a ca , p ac , a c a p p c , a a c a ac a a a c c . I b a p a c a a a c a SA p p a a a [54, 55, 59, 60, 89, 90]
TCA	10 30%. S p ca p . O 35 50% - p p . P 1 2 , >13 . P a p	Ma ca ca a PIH a , b ca [53, 58 60, 90]
T	1 5%. S p ca p . T a 1% app 4 c a , 12 [91, 92]	
MA	S p ca p . MA a 30 50% app b a a a ac a a 2%	A a ab a a ac ba a 2 10% a c b a a C a E. L a a c c a [53, 93]
P c ac	App c a b ca b p a c a acc a c . 5 6 p a ac	N a a . Sa a c a . N a , b , ca [53, 58, 94]

GA c c ac , *HQ* , *MA* a c ac , *LA* Lac c ac , *PIH* p a a p p a , *SA* a c c ac , *TCA* c ac c ac

ALGORITHM FOR INDIAN MELASMA PATIENTS

India is a country of multiple ethnicity and origin, covering a wide range of skin types. Melasma is found more frequently in Fitzpatrick type III–VI skin [48]. Based on Pigmentary Disorders Academy (PDA) recommendations for melasma treatment for dark-skin types and a thorough review and grading of the literature on evidence-based studies (listed in Table 8) [48, 61] an algorithm is proposed in Fig. 1 to treat Indian melasma patients. All treatments included and their hierarchy in the algorithm is based on the grading of the associated clinical studies according to the US preventive services

T 5 L c a c a a p a c

C	P	L	S	R
S p ca p	P c ac	E p p	C	[53]
	Lac c ac	U c a	B	[87, 88]
	G c c ac	N - a c	A	[55, 58, 59, 72, 89, 90, 94 96]
	Sa c c ac	U c a	B	[54]
	J ’	U c a	B	[97]
S p ca- p	P c ac	E p p	C	[98]
M - p p	T c ac c ac	U c a	B	[96, 97]

A: T c pp p c , B: T a c pp p c , C: T p c pp p c

T 6 C paa c ca p a a a [53]

R	S	T	P ,	T	R
Ka a a. [89]	R, O	55 75% GA . 10 15% TCA	100	E 15 a	R p a TCA a c pa GA, b c TCA
K a. [90]	O, SF	1% p . 70% GA	10	B 12	D c a MASI, c b
S a a. [87, 88],	O, SF	92% p ac c ac . J ’	30	E 3 a 5	S a ca ca p b
Sa a. [97]	O, SF	M J ’ + 15% TCA . 15% TCA	20	E 10 a 8	B p c b a p
K a a T pp a [94]	R, O	20 35% GA . 10 20% TCA	40	E 15 a 12	Ab 75% p b
S b a S b [96]	O, SF	70% GA . a a C	14	6	B a C

GA c c ac p , *MASI* a a a a , *O* p , *R* a , *SF* p ac , *TCA* c ac c ac p

T 7 T a a a

T	M	T	C
QS N :YAG La 1,064 (- c a)	P a a c a a c . A ac c c . S b- c a c cc - c . D a c a a	10 , c	E a, . A a (6) b 1 2 a a a . T a c a . P -c b a c a a c [91, 96]. PIH a b c a a b [91, 99]
C b a QS N :YAG 1,064, ac a CO_2 a	La , a a c a a	10 , 2 3	P a a . C c a a - a ca a a a . Ma a c a b ca a
IPL	Sa a a		E c a ac a a A a a [56, 67]
C b a IPL QS N :YAG a 1,064 (- c a)	Sa a a	1 IPL c a a a a b 4 5 QS N :YAG a a 2- a	Ra - a a b - b [67 69]. T a c a

IPL , *Nd:YAG* - a a , *PIH* a a a , *QS* Q c

task force levels of evidence for grading clinical trials [70].

The key considerations in developing the algorithm are: the Fitzpatrick skin types susceptible to melasma in the Indian population, the severity of melasma, the sensitivity of patients to active ingredients of medication, the patient treatment history, any existing skin condition (besides melasma), possible therapy-related AEs such as PIH, exogenous ochronosis, blotchy depigmentation, irritation, erythema; and the probability of pigment recurrence after stopping treatment, i.e., prognosis indicators. The darker skin types tend to be highly sensitive to treatment agents, for example, ochronosis on HQ treatment, sensitization to KA, and skin irritation reactions to peeling agents like GA. In addition, darker skin types are more prone to PIH post-treatment and have a greater chance of relapse [71]. With these considerations in mind, darker skin types, which are commoner among

T 8 L a a c a a ap

T	L ▼ ▼	Q ▼	R
T p ca			
2% HQ	II	C	[83]
4% HQ	I	B	[27, 43, 78, 85]
0.1% (RA)	I	B	[20, 100]
0.05% RA	I	C	[92]
0.05% I	II	C	[92, 101]
4% *N*-ac -4-*S*-C a p	III	C	[101, 102]
5% HQ + 0.1 0.4% RA + 7% LA/10% AC	III	C	[102, 103]
3% HQ + 0.1% RA	III	C	[102, 103]
2% HQ + 0.05% RA + 0.01% c ac	I	A	[38, 39, 41, 74, 85, 103, 104]
2% HQ + 0.05% RA + 0.01% a a (KF)	III	C	[55, 86]
2% HQ + 0.05% RA + 0.01% a a (KF + 30 40% GA p)	III	B	[55, 86]
5% HQ + 0.1% RA, a 1% c	III	C	[32, 33]
4% HQ + 5% GA	II	B	[104, 105]
4% KA + 5% GA	II	B	[98, 99]
2% KA + 2% HQ + 10% GA	II	C	[83, 84]
2% HQ + 10% GA	II	C	[83, 84]
4% HQ + 10% GA	I	B	[105, 106]
20% A a c ac	I	B	[42, 43]
20% A a c ac + 0.05% RA	III	C	[106, 107]
V a C p	II	C	[107, 108]
A ap a	II	B	[99, 100]
C ca p			
10 50% GA	II /III	C	[53, 59]
10% + 2% HQ + 20 70% GA	II	C	[56, 58]
20 30% GA +			

Table 8 c

T	L	Q-	R
50% GA + 10% KA	III	C	[109, 112]
La ap (+ c ca p + p ca ap)			
Q- c b	IV	C	[110, 113]
P CO2 + Q- c a a	IV	C	[67, 68]
Q- c a a a	IV	C	[69, 70]
Q- c a a a + 15 25% TCA p + J ’	III	C	[111, 114]
E b : YAG	III	D	[112, 115]
D ab a	II	E	[76, 113]

I acc a c US p c a c c a c ca a . R p c p [48]

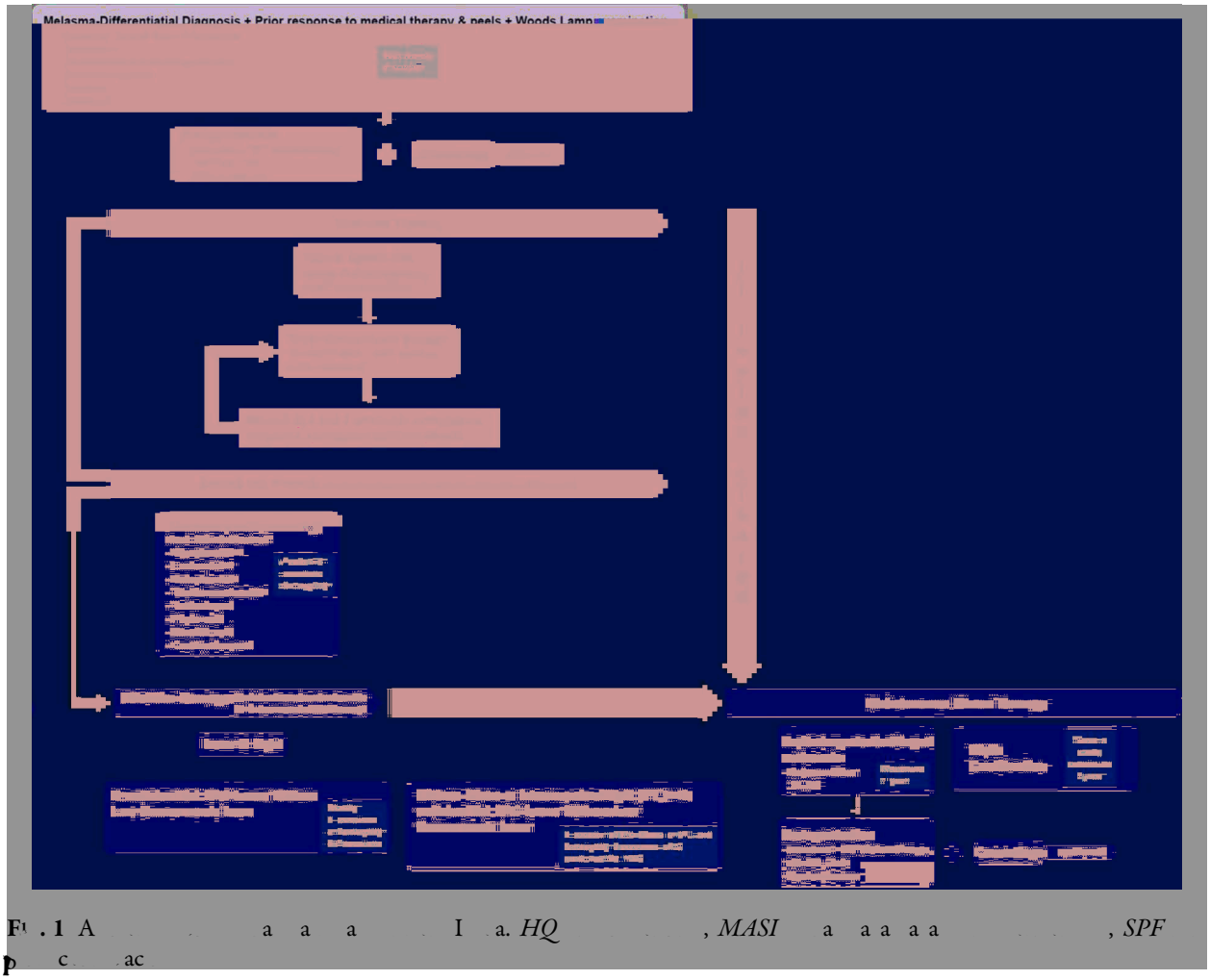
A: T c pp p c , B: T a c pp p c ,
C: T p c pp p c , D: T a c pp c
p c , E: T c pp c p c

AC c331(the3ac795I-(s)]0220985TD[(of)-334,IIf TA*(T1991137f)- -154

Indian people, are recommended longer treatment periods, with lower concentrations of those treatment agents that can induce PIH or irritation, followed by longer maintenance periods to prevent recurrence of pigmentation and melasma. We have found that treatments like laser therapy, although described for all skin types in literature, are in fact not suitable for Indian skin as PIH and relapse occurs frequently once treatment is stopped in spite of maintenance therapy. However, light therapy does have some value in Indian patients.

In the opinion of the authors, broad-spectrum sunscreen use during and post-treatment is mandatory, along with protective clothing and hats. Experts recommend the fixed triple combination as the first-line therapy for all melasma types and degrees of severity, and dual combinations or single agents should be considered only when it is unavailable or patients have sensitivity to the ingredients [48]. In such cases, we suggest dual-combination therapy (e.g., HQ + GA) or monotherapy (e.g., 4% HQ, 0.1% retinoic acid, or 20% AA). For moderate or severe melasma which does not respond to first-line treatment, options for second-line therapy include peels either alone or in combination with topical therapy.

In the opinion of the authors, some patients will require therapy to maintain remission status and a combination of topical therapies should be considered. A minimum of four sessions of a given peel are suggested before changing to an alternative therapy. It is to be noted that for Indian skin types, especially Fitzpatrick types IV–VI, the concentration of certain agents should be reduced; 5% HQ should be avoided for Indian patients as PIH and irritation are more likely at higher



F . 1 A a a a I a. *HQ* , *MASI* a a a a a , *SPF* p c ac

concentrations. Because of the risk of prolonged hyperpigmentation, medium-depth peels like ≥35% TCA should be conducted with caution in patients with dark-skin types; deep peels should not be used in these patients. Furthermore, chemical peels are generally used to treat only the epidermal and mixed forms of melasma, as an attempt to treat with deep peels often leads to unwanted complications like hypertrophic scarring and permanent depigmentation. There are ample studies on the effect of GA peels on ethnic skin [55] (Table 9) and hence make for a recommended choice of treatment. In most of these studies, there was a moderate improvement achieved in almost one-half of the patients [58, 59, 72, 73].

Lasers should rarely be used in the treatment of melasma and, if applied, it is important to consider skin type. The mode-toning laser treatment is generally recommended in all skin types and its major advantage is that it destroys melanin without cell damage. Both QS low fluence and IPL are effective for recalcitrant melasma, when patients are non-responsive to other treatments, or when patients are intolerant of other treatment medications. The combination of IPL with QS laser gives a rapid resolution of mixed-type melasma with possible long-term benefits [67–69]. Fractional non-ablative lasers can be considered only if all other modalities fail. Ablative lasers should not be considered.

T 9 S a a c [53]

R	N- >	P T	R
L a T a [58]	10 A a ( )	20 70% GA	N a ca ca
G [54]	6 (a ac a c p USA)	20 30% SA	M a p 66% pa
Ja a a a. [59]	25 I a	50% GA S c SPF 15, 10% GA	46.7% p a, 27.8% , 0% a
G a R [73]	15 I a	S a GA p	G a p
S a a. [87]	20 I a	92% LA	S ca p a 12 pa c p
G a Sa a [72]	20 I a	S a GA T p c b a p a c	>50% p a pa

GA c c ac , *LA* ac c ac , *SA* a c c ac

Patient consent and a photograph of the condition must be obtained prior to therapy. As important as actual therapy is proper patient counseling, and an understanding of the psychosocial impact on the patient and of his/her condition leading to low quality of life [74, 75]. This is likely to lead to a better patient compliance and an adherence to the regimen. It has been reported in Indian patients that overuse of certain treatment modalities such as mometasone-based therapies leads to undesirable fallouts [47, 49].

The recommendation is to use an alternative triple-combination cream, better suited for Indian patients, i.e., 2% HQ, 0.05% tretinoin, and 0.01% of the mild steroid fluocinolone acetonide cream. Another option is to replace the mometasone-based triple combination after 4–8 weeks, with a fluocinolone or a hydrocortisone-based one for a further 3- to 6-month period. As discussed earlier, this cream is safe and effective based on extensive clinical studies. The gradual withdrawal of the therapeutic agent is also a consideration and is achieved by decreasing doses of the active agent. The proposed algorithm for Indian patients is presented in Fig. 1.

T 10 Ba p ac

F
P p III VI: a a a / a
G c a a a p p [3, 6, 8–10]
L - a a p ≥2 a a
H p c a
T a b ≥2 p c a
L - - a [46, 47]
Oc [76, 114]
M - p a a [115]

BAD PROGNOSIS INDICATORS

There are several conditions that determine the outcome of treatment in melasma since its

etiology is multifactorial. Several factors predict potential failure of treatment (listed in Table 10). Moin et al. [3] found a statistically significant relationship between melasma and ethnicity, and phototype and grade of parity. Exogenous ochronosis has also been reported to be being misdiagnosed as a melisma treatment failure [76]. However, these prognostic factors lack sufficient scientific evidence.

CONCLUSION

Here, the Indian dermatologists panel has graded the results of safety and efficacy of various melasma therapies from clinical trials conducted worldwide (Table 7) applying the quality and level of evidence based on5529 -1.49663(e12.4(v)-2.t)-37913.8(u3k-270.Jfu3k-270.J0veted)-d

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