MELASMA
A Challenging Problem

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INCIDENCE & IMPACT

- Melasma is a very common skin disorder.
- Though it can affect anyone, young women are at greatest risk. It is more common in dark skins.

The domains most adversely affected by melasma :

- Social life
- Emotional well—being.

How Long does Melasma Last

Report	n	Age	Age of onset	Mean duration in years
Guevara et al 2003	39	38 (28-42)	29	9 (3-14)
Guevara et al 2001	6	39 (35-55)	29	10 (6-20)
Sanchez et al 1981	76	39	29	10
Hurley et al 2002	21	40 (23-56)	29	11 (2-26)
Ennes et al 2000	48	19-55		0.5-28

Quality Of Life (QoL)

- Treatment with combination cream for 8 weeks in 1076 patients
- QOL assessed using a skin discoloration impact questionnaire
- **Results after treatment:**
  - Less embarrassed: 64%
  - Used fewer cosmetics: 52%
  - Less effort to hide skin: 56%
  - Felt younger: 60%
  - Felt more attractive: 61%

Balkrishnan R, et al, J Drugs Dermatol 2004; 3:377-81

AETIOLOGY

- Melasma develops due to a combination of **genetic, hormonal and sun induced factors.**
- Because of melasma's relation to pregnancy and oral contraceptives, it is thought that estrogen contributes to its development in predisposed persons. It is thought that **female sex hormones** causes melanocytes to produce and deposit excess pigments.
- **Unknown factors**, when it arises in apparently healthy, normal, non-pregnant women.

Melasma in Males

- Estrogen is not essential to the development of melasma, however, as men may also be affected.
- Female: Male= 20:1.
- Scented or deodorant soaps, toiletries and cosmetics – a phototoxic reaction.

ULTRAVIOLET RADIATION

A factor that does seem to be essential to the development of melasma is sunlight.

§ **Both ultraviolet A (UVA) and ultraviolet B (UVB)** are believed to contribute to the formation of melasma in predisposed persons.

PATHOGENESIS

UV radiation induces

–Melanocyte proliferation, migration, melanogenesis.

—Production of multiple cytokines (IL 1, endothelin 1, alpha MSH) by keratinocytes which upregulate melanocyte proliferation and melanogenesis.

••Korean study of lesional and perilesional biopsies from 10 women (Im S, BJD 2002; 146:155)

—Staining for alpha MSH was higher in lesional skin.

—Sustained overexpression of MSH in lesional skin after UV exposure may be a significant factor for development of melasma

Types of Melasma

Epidermal

- ❑ Well-defined border
- ❑ Dark brown colour
- ❑ Appears more obvious under Wood's light
- ❑ Responds well to treatment

Dermal

- ❑ Ill-defined border
- ❑ Light brown colour
- ❑ Unchanged under Wood's light
- ❑ Responds poorly to treatment

Mixed

- ❑ Combination of light and brown patches
- ❑ Partial improvement with treatment

Melasma—Histopathology

- Epidermal melasma in 70% (more responsive to treatment)
- Dermal melasma in 10--15 % (less responsive to treatment)
- Mixed melasma in 20 %
- However, dermal melanophages was present in all patients with epidermal melasma on exam in one study of 11 patients

Grimes PE et al, Am J Dermatopathol 2005

Treatment

- **Start gently.** Harsh treatments may result in an irritant contact dermatitis, and this can result in PIH.

- **A COMBINATION of many measures is NEEDED.**

Management Guidelines

1. Pharmacologic Therapy
2. Chemical Peels
3. Microdermabrasion
4. Laser Therapy/Light therapy
5. Cryotherapy
6. Cosmetic Camouflage

TOPICAL MEASURES

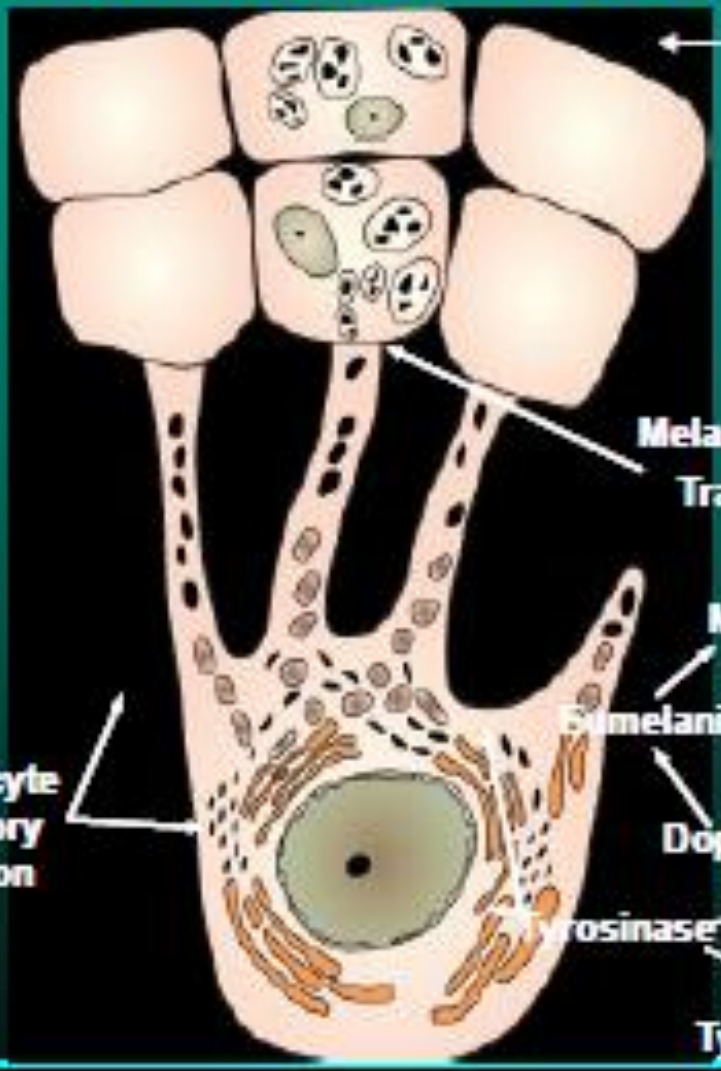
1- Topical medications aiming at:

- Decreasing proliferation of melanocytes or formation of melanin.
- Increasing removal and degradation of melanin.
- Blocking transfer of melanosomes.
- Protecting from ultraviolet light.
- Preventing inflammatory process.

General Guidelines

General	Sun Protection
❑ Discontinuing hormonal contraception. ❑ Use of a mild cleanser, and if the skin is dry, a light moisturiser.	❑ Year-round sun protection. ❑ Broad-spectrum anti-UV A and B sunscreens with physical blocking agents like ZnO and TiO2 (SPF 30) (refelctant). ❑ Alternatively, use a make-up containing sunscreen.

Understanding Dyschromias: The Epidermal Melanin Unit



Removal of pigment in superficial layers

Glycolic acid
Salicylic acid

KERATINOCYTES

Sunscreens

MELANOCYTE

Corticosteroids

Melanocyte Secretory Function

Melanosome Transfer

Tretinoin

Melanin

Eumelanin

Pheomelanin

Dopaquinone

Tyrosinase

Dopa

Hydroquinone

Tyrosine

TOPICAL APPLICATIONS

1- Preventing new pigment formation.

Bleaching creams inhibit the formation of melanin by the melanocytes. They include:

- **Hydroquinone** 2-4%, for 2 to 4 months. This sometimes causes stinging and redness.
- **Azelaic acid** can be used longterm, and is safe even in pregnancy. It may sting.
- **Kojic acid**.

Hydroquinone

The mainstay of therapy for melasma is hydroxyquinone (HQ)

It decreases melanin formation by inhibiting tyrosinase.

HQ also affects the membranous structures of melanocytes and eventually causes necrosis of whole melanocytes.

Two randomised double-blinded studies showed that HQ is effective for melasma with improvement in 76.9% to 96.3% of the patients.

It was reported 40% of patients achieved complete clearance with HQ compared with 10% with placebo.

However, adverse effects are not uncommon with HQ, mainly contact dermatitis, less commonly ochronosis & conffetti-like depigmentation.

Kligman/Willis Formula

In 1975, Kligman and Willis developed a formula containing three components: **5% HQ, 0.1% tretinoin and 0.1% dexamethasone** to treat pigmentation in a hope that individual components acted together to improve efficacy and minimize adverse reactions.

Kligman/Willis Formula

- **Proposed mechanisms of action:**

– Tretinoin reduces atrophogenic effects of steroid, facilitates epidermal penetration of hydroquinone and reduces melanosome transfer, and inhibits transcription of the key melanin synthesis enzyme tyrosinase.

– Steroid helps reduce irritation from tretinoin and decreases pigmentation on its own, anti-metabolic effect on melanocytes, resulting in a decreased epidermal turnover and thus produce a mild pigment-reducing effect.

– Results significantly less favorable if any one component was omitted

– No cases of atrophy were seen

Kligman AM, Willis I. Arch Dermatol 1975;111:40-48

Topical corticosteroid

Sometimes a topical corticosteroid such as hydrocortisone is prescribed, which works quickly to fade the colour and has an additional benefit of reducing the likelihood of a contact dermatitis caused by other agents.

Side effects: ATROPHY.

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.

Caution is required in its use as kojic acid is a known sensitizer

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.

AA treatment used in case of intolerance to HQ.

Adjunctive therapeutic agents for melasma

- Tranexamic acid
- Vitamin C
- Vitamin E
- Soybean extract
- Topical liquiritin
- Licorice extract
- Gigawhite
- Bearberry extract
- Pepper mulberry extract
- Arbutin
- Indomethacin
- Niacinamide
- Nicotinic acid
- 4-N butylresorcinolmercury
- Melawhite

Tranexamic acid

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

For Recalcitrant Melasma = Topical Therapy +

- Chemical Peels
- Lasers
- IPL
- Microdermabrasion
- Cryotherapy

Peeling off the pigment

- Salicylic acid creams
- Topical alpha hydroxyacids including glycolic acid and lactic acid, as creams or as repeated superficial chemical peels.
- Topical retinoids, such as tretinoin. This works in several ways to improve skin colour, but can be hard to tolerate and might cause dermatitis.

GLYCOLIC ACID PEELS

GA Peels & Hydroquinone for Melasma

- 20 Hispanic women with epidermal melasma,8 week study.
- Glycolic acid peels every 2 weeks X 4 (20% X 2 peels, 30% X 2 peels) applied to one side of face only.
- **VS:** Twice daily full face application of 4% hydroquinone

- Mexameter results:
  - Both sides improved significantly
  - NO SIGNIFICANT DIFFERENCE between both sides

Hurley ME, et al., Arch Dermatol 2002; 138:1578

Salicylic Acid Peels

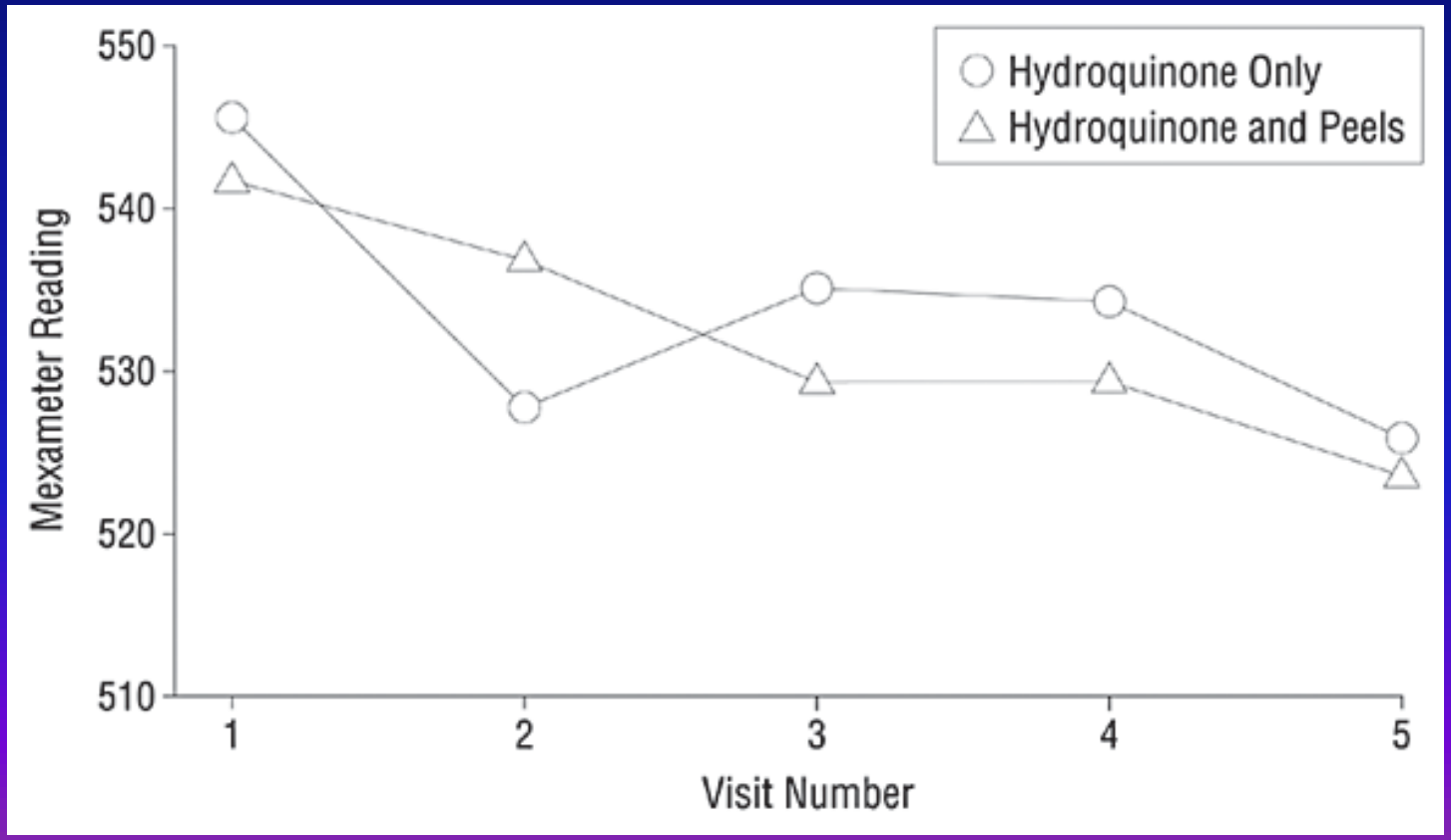
Salicylic Acid Peels for Melasma VS HQ

Randomized, Split--Face, Investigator Blinded, Controlled Trial

- 20 patients,
- Hydroquinone 4% cream to both sides of face
- Four salicylic acid peels, once every 2 weeks
- First 2 peels--20% SA, second two peels--30% SA
- 8 week follow up period
- Results : Both sides improved
  - MASI scores showed NO SIGNIFICANT DIFFERENCE between both sides

Kodali et al, JAAD

Chemical Peels vs Hydrouinone



Various Peels & Combinations

- 55–75% GA / 20–35% GA
- 10–15% TCA
- Jessner’s
- Modified Jessner’s + 15% TCA
- **TCA peel: shows side effects**

- **Medium-depth should be avoided in patients with dark skin.**
- **Biweekly for 5-8 sessions mmaintenance sessions or repeat sessions are necessary**

Official publications of the Association of Cutaneous surgeons of India (ACSI)
Journal of Cutaneous and Aesthetic Surgery

J Cutan Aesthet Surg. 2012 Oct-Dec; 5(4): 247–253.
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Chemical Peels for Melasma in Dark-Skinned Patients

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Abstract

Melasma is a common disorder of hyperpigmentation, which has a severe impact on the quality of life. Inspite of tremendous research, the treatment remains frustrating both to the patient and the treating physician. Dark skin types (Fitzpatrick types IV to VI) are especially difficult to treat owing to the increased risk of post-inflammatory hyperpigmentation (PIH). The treatment ranges from a variety of easily applied topical therapies to agents like lasers and chemical peels. Peels are a well-known modality of treatment for melasma, having shown promising results in many clinical trials. However, in darker races, the choice of the peeling agent becomes relatively limited; so, there is the need for priming agents and additional maintenance peels. Although a number of new agents have come up, there is little published evidence supporting their use in day-to -day practice. The traditional glycolic peels prove to be the best both in terms of safety as well as efficacy. Lactic acid peels being relatively inexpensive and having shown equally good results in a few studies, definitely need further experimentation. We also recommend the use of a new peeling agent, the easy phytic solution, which does not require neutralisation unlike the traditional alpha-hydroxy peels. The choice of peeling agent, the peel concentration as well as the frequency and duration of peels are all important to achieve optimum results.

KEYWORDS: Chemical peels, dark skin, melasma

INTRODUCTION

MICRODERMABRASION

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Dermabrasion and microdermabrasion should be undertaken very cautiously; damage to the melanocytes may increase pigment production and darken the melasma.

LASER THERAPIES

- Laser resurfacing – results may be unpredictable.
- Newer fractional lasers may prove safer.

Destroying the pigment with pigment laser or intense pulsed light device – this is possibly the best treatment for a quick result but several treatments may be necessary.

Laser /IPL Therapy

- Response to treatment unpredictable
- Pigmentation frequently recurs.
- PIH is common
- Hence, a maintenance schedule has to be continued

Erbium: YAG Laser Resurfacing

Erbium: YAG Laser Resurfacing for Refractory Melasma

- 10 female patients, skin types 2--5, with melasma unresponsive to bleaching agents and chemical peels.
- **Full face resurfacing** using erbium:YAG laser at 5.1--7.6 J/cm2
- Marked improvement immediately afterwards
- All had **post--inflammatory hyperpigmentation** 3--6 weeks afterwards, which was as severe or worse than the original melasma
- All then required glycolic acid peels every 2 weeks along with azelaic acid for several months to improve pigmentation
- The use of this laser therapy is recommended only for recalcitrant melasma

Manaloto RMP, Alster T, Dermatol Surg 1999; 25:21.

Q-SWITCHED Nd-YAG

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Split-face randomized study comparing combination QS-Nd:YAG laser and 2% hydroquinone with topical treatment in dermal or mixed-type melasma.

Twenty-two patients were treated with 1,064-nm QS-Nd:YAG laser, 6-mm spot size, 3.0- to 3.8-J/cm2 fluence for five sessions at 1- week intervals.

CONCLUSION: QS-Nd:YAG laser treatment for melasma in Asians produced only temporary improvement

Common complications: hypopigmentation, melasma recurrence, and

Rebound und hyperpigmentation.

Watanakrai et al, Dermatol Surg 2010;36:76–87

Fractional photothermolysis (FP)

Eight female patients using FP (1,550nm Fraxel SR laser), two to seven treatments at 3- to 8-week intervals.

RESULTS: greater than 50% clinical improvement in melasma in five of eight patients.

Follow-up assessments : sustained efficacy in five patients. Recurrence in three patients.

Initially all patients had good results, except for one patient who achieved only 25% improvement. No significant adverse effects were noted.

CONCLUSIONS FP is a safe and effective treatment for refractory melasma, with long-term remission.

Katz et al, Dermatol Surg 2010;36:1273–1280.

Laser /IPL Therapy

Type of laser	Mechanism	Treatment mode
QS Nd:YAG Laser 1,064 nm (low-fluence mode laser toning)	Photothermolysis of melanin in melanosomes in the melanocytes and keratinocytes. Also photoacoustic effect. Sub-cellular selective photothermolysis occurs in the low-fluence mode. Destroys melanin without cell damage	10 sessions, once weekly
Combination of QS Nd:YAG 1,064, with the fractional CO_2 laser	Laser toning, using a large spot size with very low fluence giving multiple passes at frequent intervals	10 sessions, every 2–3 weeks
IPL	Same as laser	–
Combination of IPL with QS Nd:YAG laser 1,064 nm (low-fluence mode laser toning)	Same as laser	1st session IPL for clearing epidermal melasma followed by 4–5 sessions of QS Nd:YAG laser at 2-week intervals

Applying Cosmetic Camouflage

Bad Prognosis Factors

Phenotype III–VI: dark hair and/or dark skin

Genetic and familial predisposition

Long-term melasma in spite of years of treatment

History of procedural interventions

Treated by many physicians

Long-term self-treatment with steroids

Ochronosis

Mixed-type melasma

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EVIDENCE-BASED REVIEW

Treatment of Melasma with Topical Agents, Peels and Lasers: An Evidence-Based Review

Shelly Rivas · Amit G. Pandya

Published online: 24 July 2013

Abstract
Background Melasma is an acquired disorder of hyperpigmentation occurring on the face and predominantly affecting women of childbearing age. It is a chronic, often relapsing condition with a negative impact on quality of

their efficacy and long-term safety. Adverse events associated with treatment were mild and short-lasting and included skin irritation, dryness, burning, and erythema. The data could not be statistically pooled because of the heterogeneity of treatments and lack of consistency across study designs.

Abstract

Background Melasma is an acquired disorder of hyperpigmentation occurring on the face and predominantly affecting women of childbearing age. It is a chronic, often relapsing condition with a negative impact on quality of life. Current treatments for melasma are unsatisfactory.

Objective The aim of this article was to conduct an evidence-based review of interventions available for the treatment of melasma.

Methods A systematic literature search was performed using PubMed and the keywords 'melasma' or 'chloasma' in the title. The search was further refined by using a filter for 'controlled clinical trials' and 'randomized controlled trial'. The included studies were used to develop recommendations for treatment.

Results The electronic search yielded a total of 80 citations. Forty studies were included in this review, which had a total of 2,912 participants. Three different therapeutic modalities were investigated—topical agents, chemical peels, and laser and light therapies. Topical depigmenting agents were found to be the most effective in treating moderate-to-severe melasma, with combination therapies, such as triple-combination therapy (hydroquinone, tretinoin, and fluocinolone acetonide), yielding the best results. Chemical peels as well as laser and light therapies were found to have moderate benefit but more studies are needed to determine their efficacy and long-term safety. Adverse events associated with treatment were mild and short-lasting and included skin irritation, dryness, burning, and erythema. The data could not be statistically pooled because of the heterogeneity of treatments and lack of consistency across study designs.

Conclusions Topical combination therapies were found to be more effective than monotherapy. Triple combination therapy was found to be the most effective, but approximately 40 % of patients develop erythema and peeling. Chemical peels and laser and light therapies produced mixed results, with increased risk of irritation and subsequent hyperpigmentation, particularly in darker-skinned individuals. Hence, current treatments available for melasma remain unsatisfactory. Many of the studies lacked long-term follow-up. Limitations of current literature include the heterogeneity of study designs, small sample sizes, and poor follow-up rates. Additional evidence for the effects and role of sunscreens is needed. Categorization or stratification of demographic data should also be included in future studies, such as age, melasma type, and duration of melasma prior to initiation of treatment. Patient's perception of improvement versus investigator's assessment of improvement should also be included in future studies and standardized methods of study design and assessment of outcomes are needed to form definitive conclusions on the efficacy of different treatment modalities.

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1 Background

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