Treatment of Pigmentary Disorders

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Disorders of Hyperpigmentation

- Fitzpatrick skin types I-III
  - Mottled hyperpigmentation (photodamage)
  - Solar lentigines
- Fitzpatrick skin types IV-VI
  - Melasma
  - PIH
  - Age-related hyperpigmentation

Melasma: Quality of Life

- Negatively impacts QOL - social life, recreation & leisure, emotional well being
- 65% of patients were bothered all or most of the time
- 55% were frustrated
- 57% were embarrassed
- 42% said it influenced interpersonal relationships
- 43% felt unattractive


Cosmetic Concerns in Women of Color

- A survey of cosmetic concerns in 100 women (81 AA, 16 Hispanic & 3 Asian)
- Mean age 41 years
- 86% = hyperpigmentation or dark spots
- 80% = blotchy uneven skin
- 77% = combination oily or oily skin
- 49% = sensitive skin
- 40% = rough skin

Grimes PE. Dermatol Clinics 2000

Therapies for Hyperpigmentation

- Protection from sun exposure
- Inhibition of tyrosinase activity
- Inhibition of melanosome transfer
- Removal of melanin
- Destruction or disruption of melanin granules


Therapies for Hyperpigmentation

- Sun protection - broad spectrum, SPF 30+, hats
- Prescription medications
- Non-prescription medications
  - Office Dispensed
  - Over the Counter (OTC)
- Adjunctive therapies
  - Chemical peels, microdermabrasion, lasers, light-based devices
Choosing a Skin Lightening Agent

- Diagnosis
- Location
- Skin type
- Formulation
- Previous treatment
- Concomitant medications
- Adjunctive therapy
- Insurance coverage
- Cost

Prescription

- Hydroquinone (HQ)
- Topical retinoids
  - Tretinoin
  - Tazarotene
  - Adapalene
- Azelaic acid

Hydroquinone

- Gold standard for skin lightening
- Discovered in the 1800s, used primarily as a photograph developer, made its way into the dermatological world as a skin lightener at the appropriate concentrations.
- Found in leaves of many plants and has antioxidant properties and is a component of glucoside arbutin.
- Inhibits the conversion of dopa to melanin by inhibiting the activity of tyrosinase (Lynde et al., 2006)

Hydroquinone

- Monotherapy
- Combination therapy
  - HQ4% microencapsulated + retinol 0.15% + antioxidant
  - HQ4% + retinol 0.3%
  - HQ4% + tretinoin 0.05% + fluocinolone 0.01%
- Compounding pharmacy
  - Hydroquinone 4-10%
  - Tretinoin cream 0.025% 20g
  - Desonide cream 0.05% 30g
  - Ascorbic acid 500 mg


Topical Retinoids

- Topical retinoids may cause melanin granule dispersion, minimizing PIH
- Retinoic acid (concentration 1µM) inhibits the induction of tyrosinase and melanogenesis
- Depigmenting effects of retinoic acid may be caused by promotion of keratinocyte proliferation and acceleration of keratinocyte differentiation

Fitzpatric and Goa. Drugs. 1991;41:780-798

Azelaic Acid

- Naturally occurring dicarboxylic acid found in wheat, barley and the human body
- Obtained from cultures of Malasseza furfur
- Inhibits tyrosinase activity, DNA synthesis, & mitochondrial enzymes, thus blocking direct cytotoxic effects towards melanocytes
- FDA approved for Acne (20% cream) and Rosacea (15% gel)
- Used off label for melasma & PIH
Efficacy and Safety of Azelaic Acid 15% Gel vs. HQ 4% Cream in the Treatment of Melasma

- 24 week, double-blind, randomized pilot study
- 30 patients, AZA gel 15% BID vs. HQ cream 4% BID
- Vanicream cleansing bar & SPF 30
- Wood's lamp evaluation, clinical photography, chromameter and laboratory testing, PGAS, MASI scores, PGAS and AEs.

Results:
- 22 patients (80% AZA group & 67% HQ group) finished the study
- Both groups had a significant improvement in mean baseline PGAS, mexameter (M & E) scores, and MASI scores
- Both groups had similar safety profiles

Callender VD, Young CM. Poster Presentation at Winter Clin 2014.

Tranexamic Acid (TA)

- Synthetic derivative of lysine
- Currently used as a hemostatic agent
- Inhibition of plasminogen/plasmin pathway, and blocking the interaction between melanocyte & keratinocyte (epidermis)
- Modulates the vascular component of melasma (dermis)
- 561 melasma patients: 250 mg po BID x 4 months with 90% improvement
- 7.1% patients with AEs: abdominal bloating/pain, N/V, headache, tinnitus, numbness, menstrual irregularities


Non-prescription: Cosmeceuticals

- Large & growing market
- Most sought after beauty treatments in the world
- A multimodal treatment approach

- Retinol & derivatives
- Arbutin & deoxyarbutin
- Kojic acid
- Licorice extract
- Vitamin C
- Glutathione
- Elagic acid
- Soy
- Aloe
- Emblica Extract
- Lignin Peroxidase
- Niacinamide
- N-acetyl glucosamine
- Oligopeptides (decapetide-12 0.01%) (p-polyglutamic acid)
- Procyanidin + Vitamins A, C & E
- Newer agents with a multi-module approach


Multimodal Skin Brightener

- Reduce Melanocyte Activation
  - Tetrahexyldecyl ascorbate
  - Ethoxyflavanols
- Reduce Melanin Synthesis (Tyrosinase)
  - Retinol
  - Linoleic acid
  - Glabridin
  - Hexylresorcinol
- Reduce Melanin Transfer to Keratinocytes
  - Niacinamide
  - Hexylresorcinol
- Remove Epidermal Melanin
  - Retinol

Multimodal Skin Brightener

- Open label case series of 6 female subjects with FST IV-V with Melasma
- Study medication was applied to affected areas of skin BID x 12 weeks; SPF 30; study visits at baseline, weeks 4, 8 & 12
- Efficacy assessments
  - Overall hyperpigmentation
  - Global improvement assessment
  - Melasma area severity index (MASI)
- Tolerability assessments
  - Digital photography
  - Self-assessment questionnaire

Results:

- Progressive improvement in pigmentation
- At week 12
  - Overall Hyperpigmentation scores & MASI scores improved by an average of 22% and 38% from baseline
  - 100% subjects showed at least 25% increase in Global Improvement
  - 67% subjects self-reported an overall improvement
- No reports of erythema, edema, scaling, burning/stinging, or itching


Sunscreens in Skin of Color (FST IV-VI)

Dual protection system of a patented combination of synergistic high efficacy sun filters + anti-oxidants to help further protect skin from UV-induced damage.

- Avobenzone 3%
- Homosalate 15%
- Oxybenzone 6%
- Octocrylene 5%
- Octisalate 5%
- Oxynex-ST
- Senna alata
- Sun Spheres
- Intelimer

Howard University Study: Prevention of sun-induced Pigmentation

- This is the first study to objectively evaluate the effect of regular sunscreen usage in subjects of SOC
- Preliminary results indicate that regular sunscreen usage in SOC improves dyschromias and lightens the skin
- A longer longitudinal study would be appropriate in the same study group to obtain more definitive data
- Clinical evidence to support use of sunscreen in the prevention and management of sun-induced pigmentation and disorders of hyperpigmentation in darker-skinned individuals

Halder R, et al.

Polypodium Leucotomes (Heliocare)

- Natural extract from the Calaguala fern leaves
- Centrall & S.A.
- Potent anti-oxidant & anti-inflammatory
- Photoprotective: inhibits the generation of reactive oxygen species (ROS) production induced by UV light

Nonsurgical Cosmetic Procedures in 2015

1. Botulinum toxin-A injections
2. Soft tissue filler injections (HA fillers)
3. Hair removal
4. Facial Chemical peels
5. Microdermabrasion

Aesthetic Considerations for SOC

- Darker skin is more prone to keloid formation and hypertrophic scarring
- Incidence ranges from 4.5%-16% compared to <1% in Caucasians
- Pigmentary changes can be more evident in darker-skinned patients
- Results from the disruption of the epidermal barrier or melanocyte stimulation
- Desired results must be discussed with skin of color patients as they may differ from Caucasian patients


Types of Chemical Peels

- Superficial chemical peels (stratum corneum to papillary dermis)
  - Glycolic acid (GA)
  - Polyhydroxy acid (PHA)
  - Salicylic acid (SA)
  - Trichloroacetic acid (TCA)
  - Tretinoin
  - Jessner’s solution

- Medium-depth chemical peels (stratum corneum to upper reticular dermis)
  - TCA 35% or greater
  - Jessner’s solution + TCA 35%
  - GA 70% + TCA 35%
  - Combination peels
    - SA<10%, LA<10%, Resorcinol <10%, Retinoic acid 0.3% (Vitalize peel)
    - SA<15%, LA<15%, Resorcinol<15%, Retinoic acid 0.5% (Rejuvenize peel)

What’s Not Safe To Use

- Chronic use of high concentrations of HQ
  - Irritant contact dermatitis, Exogenous ochronosis
  - Chronic use of low concentrations of HQ
  - Exogenous ochronosis
  - High potency corticosteroids
  - Striae, Adrenal suppression, hyperglycemia, HTN
  - Skin bleaching
  - Glutathione

- Oral, topical or IV
- Systemic skin-lightening agent
- Philippines & India
- Influence melanogenesis by:
  - A shift in the production of pheomelanin over eumelanin
  - Inhibition tyrosinase
  - Quenching of ROS and free radicals that influence tyrosinase activation


Safety concerns with Glutathione

- Easily available
- No clinical data for IV use
- AE: TEN, SJS, thyroid dysfunction, Renal failure, abdominal pain, air embolism, infection & fatal sepsis
- Hangog et al. concluded that glutathione when taking through mucosal route is safe and effective in Filipino women in both sun-exposed and sun-protected sites as 100% of their patients showed a significant decrease in melanin index from baseline.

Hangog et al., 2016

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Glutathione: FDA

- Some consumers seeking to change their skin color are turning to injectable products marketed to whiten or lighten their complexion. These products are potentially unsafe and ineffective, and might contain unknown harmful ingredients or contaminants. FDA has not approved any injectable drugs for skin whitening or lightening.
- Sold on-line, found in retail outlets & health spas
- In 2014, US Marshalls seized unapproved and improperly labeled drug products sold & distributed by Flawless Beauty, LLC
  - Relumins Advanced Glutathione kits
  - Tatiomax Glutathione Collagen kits

https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm460788.htm
Conclusions

• Effective skin lightening can be achieved **SAFELY** by implementing the following:
  
  • Sun protection
  
  • Proper use of Cosmeceuticals & prescription strength products
  
  • Combining topical with aesthetic procedures, such as chemical peels, microdermabrasion & laser surgery to enhance penetration & improve efficacy