

Common Pigmentation Disorders

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Common causes of hyperpigmentation include postinflammatory hyperpigmentation, melasma, solar lentigines, ephelides (freckles), and café-au-lait macules. Although most hyperpigmented lesions are benign and the diagnosis is straightforward, it is important to exclude melanoma and its precursors and to identify skin manifestations of systemic disease. Treatment options for postinflammatory hyperpigmentation, melasma, solar lentigines, and ephelides include the use of topical agents, chemical peels, cryotherapy, or laser therapy. Café-au-lait macules are amenable to surgical excision or laser treatment. Disorders of hypopigmentation may also pose diagnostic challenges, although those associated with health risks are uncommon and are usually congenital (e.g., albinism, piebaldism, tuberous sclerosis, hypomelanosis of Ito). Acquired disorders may include vitiligo, pityriasis alba, tinea versicolor, and postinflammatory hypopigmentation. Treatment of patients with widespread or generalized vitiligo may include cosmetic coverage, psoralen ultraviolet A-range therapy (with or without psoralens), or narrow-band ultraviolet-B therapy; whereas those with stable, limited disease may be candidates for surgical grafting techniques. Patients with extensive disease may be candidates for depigmentation therapy. Other acquired disorders may improve or resolve with treatment of the underlying condition. (*Am Fam Physician*. 2009;79(2):109-116. Copyright © 2009 American Academy of Family Physicians.)



Although most pigmentation disorders are benign or nonspecific, some disorders of skin pigmentation present cosmetic or psychological challenges to the patient, necessitating evaluation and treatment. Others may be indicators of underlying systemic disease or primary skin malignancy. Proper diagnosis of these common skin conditions will allow the physician to facilitate appropriate skin treatment and reassure the patient.

Pathophysiology

Pigmentation of skin depends on the amount and type of melanin, degree of skin vascularity, presence of carotene, and thickness of the stratum corneum. Skin hyperpigmentation usually results from an increased number, or activity, of melanocytes. Epidermal increases in melanin usually enhance with a Wood lamp, whereas dermal increases do not. Some disorders, such as melasma, may have dermal and epidermal changes and can be classified as mixed.¹

Hypopigmentation of skin may result from a reduction of melanocytes or from an inability of the melanocytes to produce melanin or properly transport melanosomes. Causes of hyper- and hypopigmentation are discussed in this article and are listed in Table 1. Certain skin pigmentation disorders are more common in certain skin types. The most commonly used system for identifying skin types is the Fitzpatrick system (Table 2).^{2,3}

Hyperpigmentation Disorders

POSTINFLAMMATORY HYPERPIGMENTATION

Postinflammatory hyperpigmentation is a common consequence of an injury or inflammation to dark skin (Fitzpatrick types IV to VI), resulting in lesions that can persist for months or years. This can be psychologically devastating to some patients. Postinflammatory hyperpigmentation may also occur after laser therapy for other pigmented skin lesions, and may be transient or long lasting. A typical example can be seen in Figure 1.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Postinflammatory hyperpigmentation may be improved with hydroquinone (Eldoquin Forte), azelaic acid (Azelex), retinoids, glycolic acid peels, and laser therapy; monotherapy is often unsatisfactory.	C	4-6
Treatment of epidermal melasma with triple therapy is more effective than treatment with hydroquinone, fluocinonide (Lidex, brand no longer available in the United States), or tretinoin (Retin-A) alone or in double combination.	B	16, 17
Chemical peels and brief cryotherapy are effective ablative treatments for solar lentigines.	C	20-22
For the treatment of localized and generalized vitiligo, high-potency steroids, topical or oral psoralens with psoralen ultraviolet A-range, and narrow-band ultraviolet-B therapies are beneficial. Vitiligo of the head and neck is most responsive to treatment.	B	32, 36-44

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

Table 1. Differential Diagnosis of Hyper- and Hypopigmentation

Hyperpigmentation	Hypopigmentation
Postinflammatory hyperpigmentation (acne, psoriasis, atopic and contact dermatitis, lichen planus, trauma, drugs, and fixed-drug eruptions)	Acquired (common)
Melasma	Vitiligo
Solar lentigines	Pityriasis alba
Ephelides (freckles)	Tinea versicolor
Café-au-lait macules	Postinflammatory hypopigmentation
Nevi	Congenital (uncommon)
Melanoma and precursors	Albinism
	Piebaldism
	Tuberous sclerosis
	Hypomelanosis of Ito

Table 2. Skin Type Classification

Skin type	Skin color	Characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel, or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	Brown; typically Mediterranean skin	Rarely burns, tans with ease
V	Dark brown; Middle-Eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

Information from references 2 and 3.



Figure 1. Postinflammatory hyperpigmentation of distal right leg following resolution of eczematous eruption.

Postinflammatory hyperpigmentation presents as irregular, darkly pigmented macules and patches at sites of previous injury or inflammation. Treatment is often difficult, requiring prolonged courses of therapy and excellent patient compliance.

Available methods of treatment for postinflammatory hyperpigmentation include hydroquinone 3% or 4% (Eldoquin Forte) twice daily, azelaic acid 20% cream (Azelex) twice daily, salicylic or glycolic acid peels, retinoids, and laser therapy. However, monotherapy often produces unsatisfactory results. In one study, the addition of serial glycolic acid peels to a hydroquinone 2%/glycolic acid 10% combination twice daily and tretinoin 0.05% (Retin-A) at bedtime resulted in faster lightening without significant adverse effects.⁴ Additionally,

retinoids such as tazarotene 0.1% cream (Tazorac) are well-tolerated and somewhat effective at reducing hyperpigmentation and disease severity.⁵

Pretreatment with topical therapies has been studied in patients with skin types I to III undergoing carbon dioxide laser resurfacing. No conclusive benefit was noted in one limited trial involving patients at the lowest risk for postinflammatory hyperpigmentation.⁶ At present, no preventative measures have proven beneficial in any skin type.

MELASMA

Melasma is a progressive, macular, nonscaling hypermelanosis of sun-exposed areas of the skin, primarily on the face and dorsal forearms. It is usually associated with pregnancy, oral contraceptives, or anticonvulsants (e.g., phenytoin [Dilantin]), or it may be idiopathic. Melasma affects women nine times more often than men, and it is more prominent in patients with skin types IV to VI (e.g., Asian, Middle Eastern, South American). It is usually asymptomatic, but it is often cosmetically distressing to the patient. Melasma typically presents in one of three patterns of distribution: centrofacial (63 percent), malar (21 percent), and mandibular (16 percent). It is usually, but not always, bilateral (*Figure 2*).

Three types of melasma exist: epidermal, dermal, and mixed. Epidermal melasma tends to be light brown, enhancing under Wood lamp examination. Dermal melasma is usually grayish in color and nonenhancing. Mixed types are dark brown with variable enhancement.

Topical treatment with hydroquinone 3% or 4%, glycolic acid 10% peel, azelaic acid 20% cream, and retinoids (e.g., tretinoin 0.05% or 0.1% cream; adapalene 0.1% or 0.3% gel [Differin]) all have some effectiveness. Combination products with hydroquinone and retinoids, glycolic acid, or topical steroids seem to be somewhat more effective. Typically, treatment must be continued indefinitely to maintain effect.⁷⁻¹⁵ In one drug-company-sponsored study, a triple-combination treatment of fluocinonide 0.01%/hydroquinone 4%/tretinoin 0.05% cream (Tri-Luma) showed significantly greater effectiveness at improving dyspigmentation than treatment with any two of these ingredients combined, with mild side effects.^{16,17} Epidermal and mixed types are not often responsive to laser therapies and frequently result in significant postinflammatory hyperpigmentation; therefore, their use cannot be recommended. However, several small studies suggest that dermal or refractory/mixed-type melasmas may be effectively treated with laser therapy or by a combination of intense pulsed-light therapy and hydroquinone with sunscreen.^{18,19}



Figure 2. Bilateral, centrofacial epidermal melasma in a 35-year-old Asian-American woman during pregnancy.



Figure 3. A 65-year-old patient with type II skin with solar lentigines (white arrow) and macular seborrheic keratoses (black arrow) on her distal forearm.

Prevention of melasma involves decreasing exposure of susceptible skin to ultraviolet (UV) rays. Opaque sunblocks with titanium dioxide or zinc oxide are most effective. There are transparent sunscreens containing these agents as well (e.g., Blue Lizard Sunscreen Sensitive SPF 30+, Neutrogena Sensitive Skin Sunblock 30+, Solbar Zinc Sunscreen SPF 38). Melasma that is induced by pregnancy or oral contraceptive use tends to fade within several months after delivery or medication cessation, so watchful waiting should be encouraged in these instances whenever possible.

SOLAR LENTIGINES

Solar lentigines (i.e., liver spots) are macular, 1- to 3-cm, hyperpigmented, well-circumscribed lesions on sun-exposed surfaces of the skin. They vary in color from light yellow to dark brown, and they often have a variegated appearance. The face, hands, forearms, chest, back and shins are the most common locations, erupting after acute or chronic UV exposure. White or Asian persons are most likely to develop solar lentigines, especially those with skin types I to III and a tendency to freckle (*Figure 3*).

Solar lentigines result from a local proliferation of basal melanocytes and a subsequent increase in melanization,

differing from freckles, which result from increased melanin production. Systemic disorders presenting with multiple lentigines may include Peutz-Jeghers syndrome (gastrointestinal hamartomas; buccal, lip, perioral, or digital macules; onset at birth or early childhood), LEOPARD syndrome (multiple lentigines, electrocardiogram abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retarded growth, and sensorineural deafness), and LAMB syndrome (multiple lentigines, atrial and/or mucocutaneous myxomas, myxoid neurofibromas, ephelides, and blue nevi). Solar lentigines must be differentiated from premalignant lesions, such as pigmented actinic keratoses or lentigo maligna. Pigmented lesions with rapid growth or change, associated symptoms (e.g., pain, itching, easy or recurrent bleeding, poor healing), atypical lesions, or those with features suspicious for melanoma should be biopsied. Full thickness excisional biopsy or punch biopsy (for large lesions or those on the face or cosmetically sensitive area) is an acceptable method of biopsy in these instances. Solar lentigines can be distinguished clinically from flat seborrheic dermatoses or pigmented actinic keratoses by the absence of epidermal hyperkeratosis. Biopsy may facilitate diagnosis in uncertain cases.

Treatment of solar lentigines consists of ablative therapies (e.g., chemical peels, cryotherapy, laser therapy) or topical therapies (e.g., hydroquinone, retinoids), and is summarized in *Table 3*. Chemical peels with 30% to 35% trichloroacetic acid (Trichlor) solution or brief

(i.e., less than 10 seconds) cryotherapy with liquid nitrogen have resulted in significant lightening of lentigines, but data are limited on long-term improvements, and recurrences are common. Additionally, cryotherapy can be painful, and prolonged treatment is associated with hypopigmentation.²⁰⁻²² Laser therapy for solar lentigines has shown benefit in at least one small, randomized controlled trial, with effectiveness superior to liquid nitrogen cryotherapy. The frequency-doubled Q-switched neodymium-doped yttrium aluminum garnet (ND: YAG) laser produced the best cosmetic results and was tolerated best. Postinflammatory hyperpigmentation is a known complication of laser therapy, and must be considered when determining the best treatment option for each patient.²²⁻²⁴

Topical therapies for solar lentigines are also available. Hydroquinone has been available for more than 30 years and is moderately effective. Adverse effects to hydroquinone include hypersensitivity, acneiform eruptions, and, rarely, ochronosis (i.e., blotchy hyperpigmentation).^{25,26} Additionally, the lightening effects of hydroquinone are slow (months), and relapse with medication discontinuation is the rule. More recently, a combination of mequinol/tretinoin (Solage) has been shown to be safe and effective in treating solar lentigines, and shows promise for prolonged maintenance.^{27,28} Retinoids such as tazarotene 0.1% cream and adapalene 0.1% or 0.3% gel may reduce the appearance of solar lentigines, but evidence is limited.^{29,30}

Prevention of solar lentigines depends on limiting sun exposure, using sunscreen regularly (especially in patients with fair skin [types I to III] and those prone to freckling), and preventing sunburns, especially after 20 years of age.

EPHELIDES

Ephelides (i.e., freckles) are small, 1- to 2-mm, sharply defined macular lesions of uniform color, most often found on the face, neck, chest, and arms. Color may vary from red to tan to light brown, and they may vary in number from a few to hundreds. Onset is usually in childhood after sun exposure. They are asymptomatic. Treatment of these lesions is not usually necessary, as they tend to fade during winter months. Cosmetically, undesired lesions can be treated similarly to lentigines (i.e., cryotherapy, hydroquinone, azelaic acid, glycolic acid peels, and laser therapy). These lesions should be differentiated

Table 3. Treatment of Solar Lentigines

Treatment	Type/dose	Side effects
Chemical peels	30% to 35% trichloroacetic acid (Trichlor)	Transient stinging, burning, pain
Cryotherapy	Liquid nitrogen	Pain, hypopigmentation with prolonged exposure
Laser therapy	Neodymium-doped yttrium aluminum garnet (ND: YAG) laser	Pain, postinflammatory hyperpigmentation, redness, textural changes, hypopigmentation
Hydroquinone (Eldoquin Forte)	3% to 4% topical	Hypersensitivity, acne, ochronosis
Mequinol/tretinoin (Solage)	2% mequinol/0.01% tretinoin topical solution	Redness, dryness, itching, sensitivity
Retinoids	Tazarotene 0.1% cream (Tazorac); adapalene 0.1% or 0.3% gel (Differin)	Redness, dryness, itching, sensitivity



Figure 4. Solitary café-au-lait macule on the right upper back identified during a routine physical examination of a 46-year-old black patient.

from juvenile lentigines (2 to 10 mm) and solar lentigines (2 to 20 mm), which usually arrive later in life.

CAFÉ-AU-LAIT MACULES

Café-au-lait macules are tan or brown macules ranging in size from 1 to 20 cm, which are present at birth or occur early in life. They are epidermal in origin, representing an increase in melanin in melanocytes and basal keratinocytes. They may be found on any body part, but often are located on the trunk (Figure 4). Ten to 30 percent of the population has an isolated café-au-lait macule.³¹

Café-au-lait macules are asymptomatic and require treatment for cosmesis only. Laser therapies and surgical excision are effective. More than six café-au-lait lesions (5 mm or larger, prepubertal; and 15 mm or larger, postpubertal) should raise suspicion for an underlying systemic disorder such as tuberous sclerosis, neurofibromatosis, Albright syndrome, or Fanconi anemia.²

Hypopigmented Lesions

VITILIGO

Vitiligo is a disfiguring skin disease resulting in loss of pigmentation. It results from an immune-mediated destruction of melanocytes. Its exact etiology is unknown. Vitiligo affects all skin types and is generally considered a cosmetic condition, but it can cause significant psychological distress, particularly to some black patients.

Vitiligo is found in 1 percent of the general population, affecting males and females equally. Family history of vitiligo is established in 25 to 30 percent of patients.³¹ Onset is often insidious, but is frequently related to a



Figure 5. Localized vitiligo of the distal leg and ankle in a 35-year-old patient.

recent stress, illness, or trauma (e.g., sunburn). Peak onset is in the second and third decades of life, with 50 percent occurring before 20 years of age.³¹

Lesions in vitiligo consist of unpigmented, sharply defined macules ranging in size from 5 to 50 mm. Some will have a rim of hyperpigmentation or erythema. Common sites of involvement include the face, neck, dorsal hands, genitalia, body folds, and axillae (Figure 5). Perioral, periorbital, periumbilical, and perianal lesions also occur.

Four types of vitiligo exist: generalized, acral/acrofacial, localized, and segmental. Generalized vitiligo involves greater than 10 percent of the body surface area. Acral/acrofacial vitiligo typically involves the face and distal extremities (i.e., the so-called “tip/lip” pattern). Localized vitiligo tends to involve a smaller body surface area and is generally stable in nature. Segmental (i.e., single dermatome or extremity) vitiligo is more often present in children and has a poorer prognosis for treatment.

Treatment of vitiligo depends on the extent of the disease and the pattern of distribution. Lesions of the head and neck tend to be most responsive to treatment, whereas those on the extremities and genitalia tend to be more recalcitrant. Vitiligo treatments are summarized in Table 4.

Treatment is multifaceted and may involve sun protection, cosmesis, topical steroids and immune

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Table 4. Treatment of Vitiligo

<i>Treatment</i>	<i>Examples and comments</i>
Sun protection	Hats, long-sleeved shirts, long pants, sunscreen
Cosmetic coverage	Concealers (e.g., Dermablend, Covermark)
Topical steroids	Topical steroid class II and III (e.g., betamethasone 0.05% [Diprolene], fluocinonide 0.05% [Lidex, brand no longer available in the United States]); head and neck most responsive to treatment
Phototherapy	Topical or oral psoralens with psoralen ultraviolet A-range, narrow-band ultraviolet-B therapy
Depigmentation	Monobenzene 20% cream (Benoquin) twice daily for six to 18 months
Surgical grafting	Mini-graft, punch-graft techniques; for localized, stable disease

modifiers, topical and oral psoralens and psoralen ultraviolet A-range (PUVA) therapy, narrow-band ultraviolet-B (UV-B) therapy, depigmentation therapy, and surgical grafting techniques.

Sun protection is important for patients with vitiligo. Sunscreens that contain avobenzone (Parsol 1789) or titanium dioxide provide broad-spectrum UV protection and should be used regularly, because affected skin is especially sensitive to sun exposure. Sun-protective clothing (e.g., wide-brimmed hats, long-sleeved shirts, long pants) will limit UV exposure as well. Cosmetic concealers (e.g., Dermablend, Covermark), topical dyes, and sunless self-tanning products (best on skin types II and

Table 5. Summary of Common Pigmentation Disorders

<i>Disorder</i>	<i>Description</i>	<i>Location</i>	<i>Etiology</i>	<i>Treatment</i>
Postinflammatory hyperpigmentation	Irregular, darkly-pigmented macules or patches	Previous sites of injury or inflammation	Trauma, inflammation	Hydroquinone (Eldoquin Forte), azelaic acid (Azelex), retinoids, chemical peels, laser therapy; combination therapy is most effective
Melasma	Pigmented, well-defined macules; light brown, brown, or gray in color	Face (63 percent centrofacial, 21 percent malar, 16 percent mandibular), forearms	Pregnancy, oral contraceptives, phenytoin (Dilantin), idiopathic	Sunscreen; combinations of: hydroquinone, retinoids, glycolic acid peels, topical steroids; laser therapy, intense pulsed light therapy for dermal lesions
Solar lentigines	1- to 3-cm macules, well-circumscribed, light yellow to dark brown, variegated color	Face, hands, forearms, chest, back, shins	Acute, chronic ultraviolet light exposure	Hydroquinone, retinoids, chemical peels, laser therapy, cryotherapy
Ephelides	1- to 2-mm, sharply defined macules, red to tan to light brown in color	Childhood onset, face, neck, chest, arms, legs	Sun exposure in susceptible persons (i.e., skin types I to II)	None needed; fades in winter months
Café-au-lait macules	Tan to brown patches, 1 to 20 cm, epidermal, present at birth or early childhood	Usually on trunk, but possible anywhere	Increased melanin in melanocytes, basal keratinocytes	Laser therapy, surgical excision; cosmetic treatment
Vitiligo	Unpigmented macules and patches, sharply defined, 5 to 50 mm, coalescent	Face, hands, forearms, neck, genitalia, body folds, periorificial	Unknown, possibly immune-mediated	Sunscreens, concealers, dyes, topical steroids, oral psoralens with psoralen ultraviolet A-range, narrow-band ultraviolet-B therapy, depigmentation, grafting

III) may reduce the disparity in pigmentation to a more acceptable level.

High-potency topical steroids (classes II and III) have been found to be beneficial in facilitating repigmentation (in limited disease), with the face and neck being the most responsive. For more extensive disease, other options (e.g., topical or oral psoralens with PUVA therapy, narrow-band UV-B therapy with or without tacrolimus [Protopic]) may prove beneficial.³²⁻⁴⁴

Depigmentation therapy with monobenzene 20% cream (Benoquin) is reserved for patients with extensive (i.e., greater than 40 percent body surface area) involvements. Treatment is twice daily for six to 18 months, and patients must be counseled that its effects are irreversible, as melanocytes are permanently destroyed. Major side effects include contact or irritant dermatitis, pruritus, xerosis, and, less commonly, conjunctival melanosis and corneal pigment deposition. Sun protection is a mainstay of post-treatment care.

Patients with stable, localized vitiligo may elect to undergo surgical treatment of medically refractory lesions (e.g., hands, lips, genitalia). Multiple punch and mini-graft treatments are available.⁴⁵

OTHER HYPOPIGMENTATION DISORDERS

Other disorders commonly associated with hypopigmentation include pityriasis alba, tinea versicolor, postinflammatory hypomelanosis (i.e., loss of melanin), atopic dermatitis, psoriasis, and guttate parapsoriasis. Additionally, it may also result from dermabrasion, chemical peels, and intralesional steroid therapy. A detailed description of these conditions is beyond the scope of this article and are described elsewhere.³¹ Table 5 provides a summary of common pigmentation disorders seen by family physicians.

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REFERENCES

1. Stulberg DL, Clark N, Tovey D. Common hyperpigmentation disorders in adults: Part I. Diagnostic approach, café-au-lait macules, diffuse hyperpigmentation, sun exposure, and phototoxic reactions. *Am Fam Physician*. 2003;68(10):1955-1960.
2. Fitzpatrick TB. *Fitzpatrick's Dermatology in General Medicine*. 4th ed. New York, NY: McGraw-Hill; 1993:966-968,1694,1984.
3. World Health Organization. Skin cancers. <http://www.who.int/uv/faq/skincancer/en/print.html>. Accessed October 31, 2008.
4. Burns RL, Prevost-Blank PL, Lawry MA, Lawry TB, Faria DT, Fivenson DP. Glycolic acid peels for postinflammatory hyperpigmentation in black patients. A comparative study. *Dermatol Surg*. 1997;23(3):171-175.
5. Grimes P, Callender V. Tazarotene cream for postinflammatory hyperpigmentation and acne vulgaris in darker skin: a double-blind, randomized, vehicle-controlled study. *Cutis*. 2006;77(1):45-50.
6. West TB, Alster TS. Effect of pretreatment on the incidence of hyperpigmentation following cutaneous CO₂ laser resurfacing. *Dermatol Surg*. 1999;25(1):15-17.
7. Erbil H, Sezer E, Tastan B, Arca E, Kurumlu Z. Efficacy and safety of serial glycolic acid peels and a topical regimen in the treatment of recalcitrant melasma. *J Dermatol*. 2007;34(1):25-30.
8. Fitzpatrick TB, Wolff K, Johnson RA, Suurmond D. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*. 5th ed. New York, NY: McGraw-Hill; 2005:350-353.
9. Leenutaphong V, Nettakul A, Rattanasuwan P. Topical isotretinoin for melasma in Thai patients: a vehicle-controlled clinical trial. *J Med Assoc Thai*. 1999;82(9):868-875.
10. Nanda S, Grover C, Reddy BS. Efficacy of hydroquinone (2%) versus tretinoin (0.025%) as adjunct topical agents for chemical peeling in patients of melasma. *Dermatol Surg*. 2004;30(3):385-389.
11. Guevara IL, Pandya AG. Safety and efficacy of 4% hydroquinone combined with 10% glycolic acid, antioxidants, and sunscreen in the treatment of melasma. *Int J Dermatol*. 2003;42(12):966-972.
12. Haddad AL, Matos LF, Brunstein F, Ferreira LM, Silva A, Costa D Jr. A clinical, prospective, randomized, double-blind trial comparing skin whitening complex with hydroquinone vs. placebo in the treatment of melasma. *Int J Dermatol*. 2003;42(2):153-156.
13. Lim JT, Tham SN. Glycolic acid peels in the treatment of melasma among Asian women. *Dermatol Surg*. 1997;23(3):177-179.
14. Espinal-Perez LE, Moncada B, Castanedo-Cazares JP. A double-blind randomized trial of 5% ascorbic acid vs. 4% hydroquinone in melasma. *Int J Dermatol*. 2004;43(8):604-607.
15. Dogra S, Kanwar AJ, Parsad D. Adapalene in the treatment of melasma: a preliminary report. *J Dermatol*. 2002;29(8):539-540.
16. Taylor SC, Torok H, Jones T, et al. Efficacy and safety of a new triple-combination agent for the treatment of facial melasma. *Cutis*. 2003;72(1):67-72.
17. Torok H, Taylor S, Baumann L, et al. A large 12-month extension study of an 8-week trial to evaluate the safety and efficacy of triple combination (TC) cream in melasma patients previously treated with TC cream or one of its dyads. *J Drugs Dermatol*. 2005;4(5):592-597.
18. Nouri K, Bowes L, Chartier T, Romagosa R, Spencer J. Combination treatment of melasma with pulsed CO₂ laser followed by Q-switched alexandrite laser: a pilot study. *Dermatol Surg*. 1999;25(6):494-497.
19. Wang CC, Hui CY, Sue YM, Wong WR, Hong HS. Intense pulsed light for the treatment of refractory melasma in Asian persons. *Dermatol Surg*. 2004;30(9):1196-1200.
20. Lugo-Janer A, Lugo-Somolinos A, Sanchez JL. Comparison of trichloroacetic acid solution and cryosurgery in the treatment of solar lentigines. *Int J Dermatol*. 2003;42(10):829-831.
21. Almond-Roesler B, Zouboulis CC. Successful treatment of solar lentigines by brief gentle cryosurgery using a Kryomed device. *Br J Dermatol*. 2000;143(1):216-218.

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22. Li YT, Yang KC. Comparison of the frequency-doubled Q-switched Nd: YAG laser and 35% trichloroacetic acid for the treatment of face lentigines. *Dermatol Surg*. 1999;25(3):202-204.
23. Todd MM, Rallis TM, Gerwels JW, Hata TR. A comparison of 3 lasers and liquid nitrogen in the treatment of solar lentigines: a randomized, controlled, comparative trial. *Arch Dermatol*. 2000;136(7):841-846.
24. Wang CC, Sue YM, Yang CH, Chen CK. A comparison of Q-switched alexandrite laser and intense pulsed light for the treatment of freckles and lentigines in Asian persons: a randomized, physician-blinded, split-face comparative trial. *J Am Acad Dermatol*. 2006;54(5):804-810.
25. Petit L, Piérard GE. Analytic quantification of solar lentigines lightening by a 2% hydroquinone-cyclodextrin formulation. *J Eur Acad Dermatol Venereol*. 2003;17(5):546-549.
26. Draelos ZD. Novel approach to the treatment of hyperpigmented photodamaged skin: 4% hydroquinone/0.3% retinol versus tretinoin 0.05% emollient cream. *Dermatol Surg*. 2005;31(7 pt 2):799-804.
27. Fleischer AB Jr, Schwartzel EH, Colby SI, Altman DJ. The combination of 2% 4-hydroxyanisole (Mequinol) and 0.01% tretinoin is effective in improving the appearance of solar lentigines and related hyperpigmented lesions in two double-blind multicenter clinical studies. *J Am Acad Dermatol*. 2000;42(3):459-467.
28. Jarratt M. Mequinol 2%/tretinoin 0.01% solution: an effective and safe alternative to hydroquinone 3% in the treatment of solar lentigines. *Cutis*. 2004;74(5):319-322.
29. Kang S, Goldfarb MT, Weiss JS, et al. Assessment of adapalene gel for the treatment of actinic keratoses and lentigines: a randomized trial. *J Am Acad Dermatol*. 2003;49(1):83-90.
30. Kang S, Kreuger GG, Tangherelli EA, et al., for the Tazarotene Cream in Photodamage Study Group. A multicenter, randomized, double-blind trial of tazarotene 0.1% cream in the treatment of photodamage. *J Am Acad Dermatol*. 2005;52(2):268-274.
31. Fathman EM, Habif TP. *Skin Disease: Diagnosis and Treatment*. 1st ed. St. Louis, Mo.: Mosby; 2001:58,184-186,308-311,469.
32. Kawalek AZ, Spencer JM, Phelps RG. Combined excimer laser and topical tacrolimus for the treatment of vitiligo: a pilot study. *Dermatol Surg*. 2004;30(2 pt 1):130-135.
33. Stulberg DL, Clark N, Tovey D. Common hyperpigmentation disorders in adults: Part II: Melanoma, seborrheic keratoses, acanthosis nigricans, melasma, diabetic dermopathy, tinea versicolor, and postinflammatory hyperpigmentation. *Am Fam Physician*. 2003;68(10):1963-1968.
34. Kumaran MS, Kauri, Kumar B. Effect of topical calcipotriol, betamethasone dipropionate and their combination in the treatment of localized vitiligo. *J Eur Acad Dermatol Venereol*. 2006;20(3):269-273.
35. Lepe V, Moncada B, Castaneda-Cazares JP, Torres-Alvarez MB, Ortiz CA, Torres-Rubalcava AB. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. *Arch Dermatol*. 2003;139(5):581-585.
36. Passeron T, Ostovari N, Zakaria W, et al. Topical tacrolimus and the 308-nm excimer laser: a synergistic combination for the treatment of vitiligo. *Arch Dermatol*. 2004;140(9):1065-1069.
37. Mehrabi D, Pandya AG. A randomized, placebo-controlled, double-blind trial comparing narrowband UV-B plus 0.1% tacrolimus ointment with narrowband UV-B plus placebo in the treatment of generalized vitiligo. *Arch Dermatol*. 2006;142(7):927-929.
38. Leone G, Pacifico A, Iacovelli P, Paro Vidolin A, Picardo M. Tacalcitol and narrow-band phototherapy in patients with vitiligo. *Clin Exp Dermatol*. 2006;31(2):200-205.
39. Valkova S, Trashlieva M, Christova P. Treatment of vitiligo with local khellin and UVA: comparison with systemic PUVA. *Clin Exp Dermatol*. 2004;29(2):180-184.
40. Arca E, Tastan HB, Erbil AH, Sezer E, Koc E, Kurumlu Z. Narrow-band ultraviolet B as monotherapy and in combination with topical calcipotriol in the treatment of vitiligo. *J Dermatol*. 2006;33(5):338-343.
41. Tjioe M, Gerritsen MJ, Juhlin L, van de Kerkhof PC. Treatment of vitiligo vulgaris with narrow band UVB (311 nm) for one year and the effect of addition of folic acid and vitamin B12 [published correction appears in *Acta Derm Venereol*. 2002;82(6):485]. *Acta Derm Venereol*. 2002;82(5):369-372.
42. Hamzavi I, Jain H, McLean D, Shapiro J, Zeng H, Lui H. Parametric modeling of narrowband UV-B phototherapy for vitiligo using a novel quantitative tool: the Vitiligo Area Scoring Index. *Arch Dermatol*. 2004;140(6):677-683.
43. Njoo MD, Westerhof W, Bos JD, Bossuyt PM. The development of guidelines for the treatment of vitiligo. Clinical Epidemiology Unit of the Istituto Dermopatico dell'Immacolata-Istituto di Recovero e Cura a Carattere Scientifico (IDI-IRCCS) and the Archives of Dermatology. *Arch Dermatol*. 1999;135(12):1514-1521.
44. Whittington ME, Ashcroft DM, Barrett CW, Gonzalez U. Interventions for vitiligo. *Cochrane Database Syst Rev*. 2006;(1):CD003263.
45. Barman KD, Khaitan BK, Verma KK. A comparative study of punch grafting followed by topical corticosteroid versus punch grafting followed by PUVA therapy in stable vitiligo. *Dermatol Surg*. 2004;30(1):49-53.