Drug-induced pigmentation

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What is drug-induced pigmentation?

Drug-induced pigmentation is a change in skin pigmentation due to a change in melanin synthesis, or the accumulation of drugs or their metabolites in the skin.

Common causes include chemotherapy, antimalarials, and nonsteroidal anti-inflammatory drugs. Hyperpigmentation is more common and results from the deposition of melanin or the implicated drug in an uneven manner, while hypopigmentation develops from melanin deficiency.

Drugs are responsible for 10–20% of acquired hyperpigmentation. Other causes include sun damage, hormonal changes, or inflammation.

- **Who gets drug-induced pigmentation?**
- Drug-induced pigmentation affects all skin types and ethnicities, but certain combinations of skin types and medications may experience more significant pigmentation effects.
- More common in women and people of Asian or African descent.
- Incidence depends on the drug in question, its dosage, and the duration of therapy.
- Drug-induced hypopigmentation is less common than drug-induced hyperpigmentation.
- A meta-analysis found that 3.2% of patients on antimalarials experienced drug-induced hyperpigmentation.

- **What causes drug-induced pigmentation?**
- Medications that can cause drug-induced pigmentation include:
- Antimalarials Chemotherapeutic agents
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Antipsychotics Amiodarone Anticonvulsants Minocycline Heavy metals.
- Kratom, a herbal substance used historically most often in South East Asia, can cause photodistributed hyperpigmentation. Its use in other parts of the world is increasing.
- The pathophysiology is not completely understood and varies depending on the drug; proposed mechanisms for hyperpigmentation include:
- Indirect toxicity to the skin/melanocyte damage — eg, bleomycin and doxorubicin melanocyte damage

- Accumulation of drug/ drug metabolites in the skin — eg, chloroquine and hydroxychloroquine
- Immune mediation or an allergic reaction resulting in inflammation and pigment deposition — eg, gold (immune-mediated reaction)
- Stimulation of melanin production — eg, oral contraceptives and hormone replacement therapy (HRT) may stimulate melanin production
- Formation of drug-protein complexes causing inflammation and melanin deposition — amiodarone is proposed to cause pigmentation this way.
- Drug-induced pigmentation may also be dictated by genetic variables. Those with polymorphisms in the *UGT1A4* gene, for instance, may be more vulnerable to chloroquine-induced pigmentation.

- **What are the clinical features of drug-induced pigmentation?**
- Clinical features vary widely depending on the drug involved, duration of treatment, and individual patient characteristics.
- Cutaneous features include:
- Hyperpigmentation- Hypopigmentation
- Mottled pigmentation: with both hyper- and hypopigmentation
- Blue-grey pigmentation: particularly in sun-exposed areas
- Orange-yellow pigmentation: particularly in the palms and soles.

- **Non-cutaneous features include:**
- Ocular changes: pigmentation in the conjunctiva or sclera
- Nail changes: pigmentation of nails and surrounding skin
- Oral mucosa changes: pigmentation of the oral mucosa results in a blue-black discolouration of gums and tongue.
- The pattern of pigmentation may suggest a particular implicated drug; localised pigmentation on the face, lip, or genitalia may suggest a resolved fixed drug eruption. Flagellate pigmentation is a feature of a bleomycin eruption.

- **What is the differential diagnosis for drug-induced pigmentation?**
- Postinflammatory hyperpigmentation
- Melasma
- Lichen planus pigmentosus
- Drug-induced photosensitivity
- Haemochromatosis
- Addison disease
- Wilson disease
- Vitamin deficiencies
- Naevus of Ota, Ito, or Hori
- Other pigmentation disorders such as idiopathic and drug-induced vitiligo

- **What is the treatment for drug-induced pigmentation?**
- **General measures**
- Discontinue the causative medication, if possible.
- Sun protection is essential to prevent the worsening of pigmentation.
- In most cases, the pigmentation will resolve over time once the medication is stopped; however, it may be prolonged or permanent.
- **Specific measures**
- Persistent pigmentation can be very challenging to treat.
- Topical therapies such as hydroquinone, retinoids, and azelaic acid may be helpful.
- Chemical peels and laser therapy can sometimes be effective.
  - Laser treatment has been successful in treating amiodarone-induced skin pigmentation, however, it can also lead to postinflammatory hyper- and hypopigmentation so should only be carried out by those with experience.

- **How do you prevent drug-induced pigmentation?**
- Avoid medications known to cause pigmentation changes in individuals with a history of drug-induced pigmentation or those at risk for developing it.
- Sun protection to prevent exacerbation of existing pigmentation changes.
- **What is the outcome for drug-induced pigmentation?**
- Prognosis is generally good, as drug-induced pigmentation typically fades over time after discontinuing the causative medication. In rare cases, the pigmentation may be permanent.

Drug/drug group	Clinical features
Heavy metals (iron, gold, silver)	Pigmentation from heavy metal toxicity may be permanent. Iron can cause dark brown pigmentation (siderosis) at an inadvertent subcutaneous injection site. Excessive gold, previously used to treat rheumatic diseases, can cause diffuse golden-brown pigmentation. Ingested silver salts may induce diffuse greyish pigmentation (argyria).
Tetracyclines (minocycline, doxycycline)	Bluish pigmentation, especially in scars. May affect nails and skin. Cumulative: pigmentation more likely on higher doses. Affects older patients more than younger ones. May take several years to clear once the drug has been stopped. More common in individuals with darker skin types.
Antipsychotics (chlorpromazine and related phenothiazines)	Bluish-grey pigmentation, especially in sun-exposed areas. Pigmentation is cumulative, and some areas may develop a purplish tint. Pigmentation of the conjunctiva in the eye may also occur, along with cataracts and corneal opacities.

Anticonvulsants	Phenytoin and carbamazepine can cause a brownish-grey pigmentation of the skin. 10% of patients develop pigmentation of the face and neck resembling melasma (clearly defined, roughly symmetrical dark brown patches). Fades after a few months when the drug has been stopped.
Antimalarials	About 25% of patients receiving chloroquine or hydroxychloroquine for several years develop bluish-grey pigmentation on the face, neck, oral mucous membranes and sometimes lower legs and forearms. Continuous, long-term use may lead to blue-black patches, especially in sun-exposed areas. Nail beds and corneal and retinal changes may also develop. This is particularly common in darker-skinned individuals.
Cytotoxic drugs	Busulfan, cyclophosphamide, bleomycin, and adriamycin have all produced hyperpigmentation to some degree. Bleomycin may induce flagellate pigmentation Banded or diffuse pigmentation of nails often occurs.

Amiodarone	Blue-grey pigmentation in sun-exposed areas (face and hands). Photosensitivity occurs in 30–57% of patients, while 1–10% show skin pigmentation. Skin pigmentation is reversible, but it may take up to one year for complete resolution after the drug has been stopped. More common in individuals with lighter skin types.
NSAIDs	Often associated with fixed drug eruptions (resolve promptly but leave a local brown pigmentation). May occur on the face, extremities, and genitalia. Commonly affect individuals with darker skin types, particularly those of African and Indian descent.

Thank You