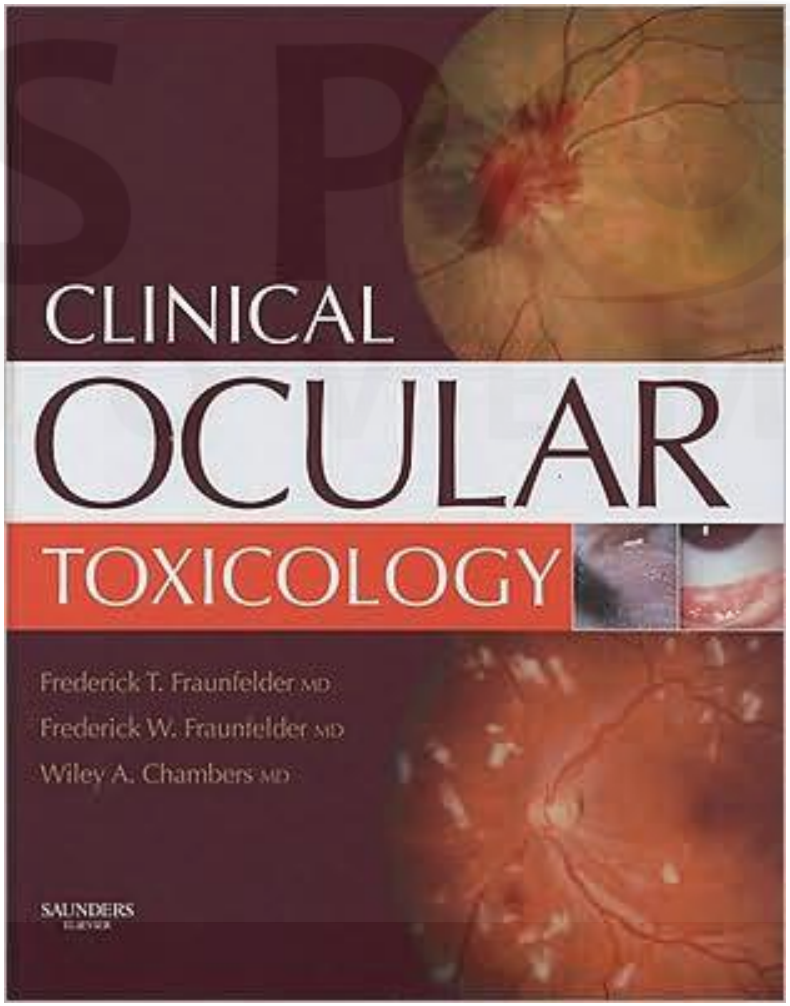
Toxicidade ocular induzida por fármacos sistémicos

Filipe Simões da Silva

HOSPITAL BEATRIZ ÂNGELO

Toxicidade Ocular



Clinical Ocular Toxicology: Drug-Induced Ocular Side Effects. Frederick T. Fraunfelder, Frederick W. Fraunfelder, Wiley A.Chambers. SAUNDERS

www.eyedrugregistry.com

Toxicidade Ocular

- Olho seco
- Córnea
- Cristalino
- Glaucoma
- Íris
- Uveíte
- Retina
- Nervo óptico

Olho seco

- Défice da camada aquosa

Table 3-6 Medications With Anticholinergic Side Effects That Decrease Tea Production

Antihypertensives
- Clonidine (α_1-blocker)
- Prazosin (α_1-blocker)
- Propranolol (β-blocker)
- Reserpine
- Methyldopa, guanethidine

Antidepressants and psychotropics
- Amitriptyline, nortriptyline
- Imipramine, desipramine, clomipramine
- Doxepin
- Phenelzine, tranylcypromine
- Amoxapine, trimipramine
- Phenothiazines
- Nitrazepam, diazepam
- Diuretics, sometimes in combination with other antihypertensive drugs

Cardiac antiarrhythmia drugs
- Disopyramide
- Mexiletine
- Amiodarone

Parkinson disease medications
- Trihexyphenidyl
- Benztropine
- Biperiden
- Procyclidine

Antiulcer agents
- Atropine-like agents
- Metoclopramide, other drugs that decrease gastric motility

Muscle spasm medications
- Cyclobenzaprine
- Methocarbamol

Decongestants (nonprescription cold remedies)
- Ephedrine
- Pseudoephedrine

Antihistamines

Anesthetics
- Enflurane
- Halothane
- Nitrous oxide

Bisphosphonates

Hormonal: estrogen replacement, androgen antagonists

Córnea- epitélio

- *Córnea verticillata*

  - opacidades cinzentas ou castanho-douradas, fusiformes

  - lípidos do epitélio basal

  - geralmente assintomático

  - reversível



Córnea- epitélio

- *Córnea verticillata*

  - Amiodarona

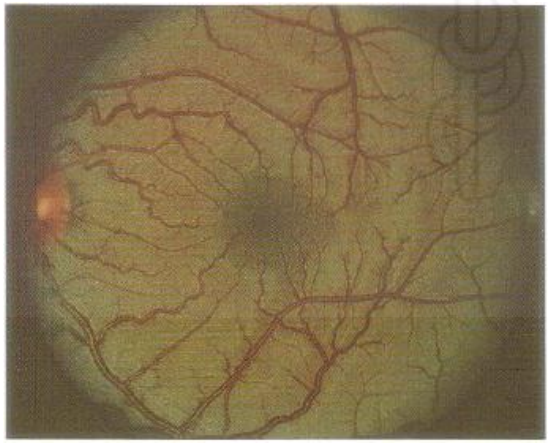
  - Cloroquina

  - Hidroxicloroquina

  - Doença de Fabry

Table 12-3 Systemic Drugs Associated With Corneal Deposits

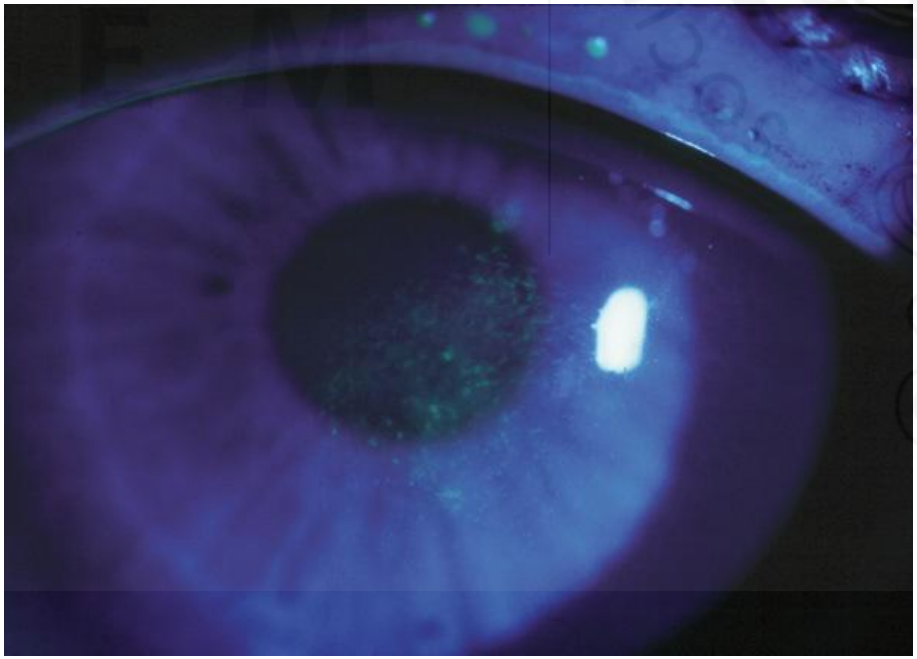
Corneal Verticillata
Aminoquinolones (chloroquine, hydroxychloroquine, amodiaquine)
Amiodarone
Atovaquone
Biaxin (clarithromycin)
Clofazimine
Phenothiazine (chlorpromazine)
Gentamicin (subconjunctival)
Gold
Ibuprofen
Indomethacin
Mepacrine
Monobenzone (topical skin ointment)
Naproxen
Perhexiline maleate
Suramin
Tamoxifen
Thioxanthines (chlorprothixine, thiothixine)
Tilorone hydrochloride



Córnea- epitélio

- Quistos epiteliais/queratopatia punctiforme

  - inibidores da síntese de ADN, i.e, citarabina



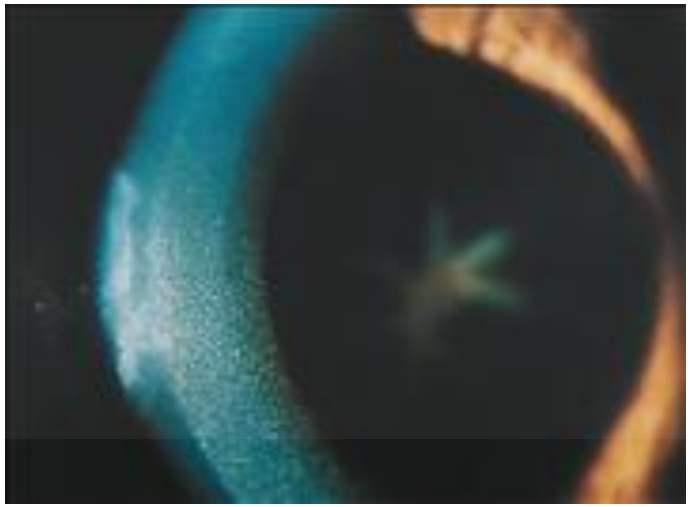
Córnea- estroma e membrana de Descemet

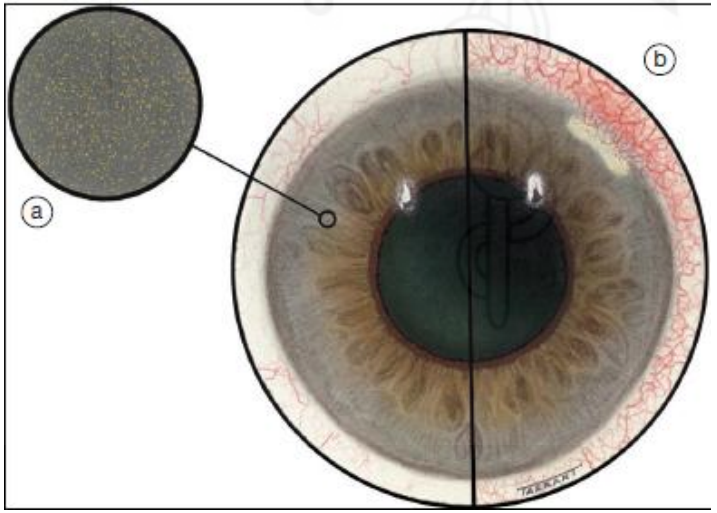
- Depósitos pigmentados

  - Clorpromazina: opacidades castanhas, granulares

  - Crisíase: sais de ouro, opacidades douradas, dose > 1 g

Stromal Deposits
Antacids
Clofazimine
Gold
Immunoglobulins
Indomethacin
Phenothiazines
Phenylbutazone
Practolol
Retinoids (isotretinoin
Silver

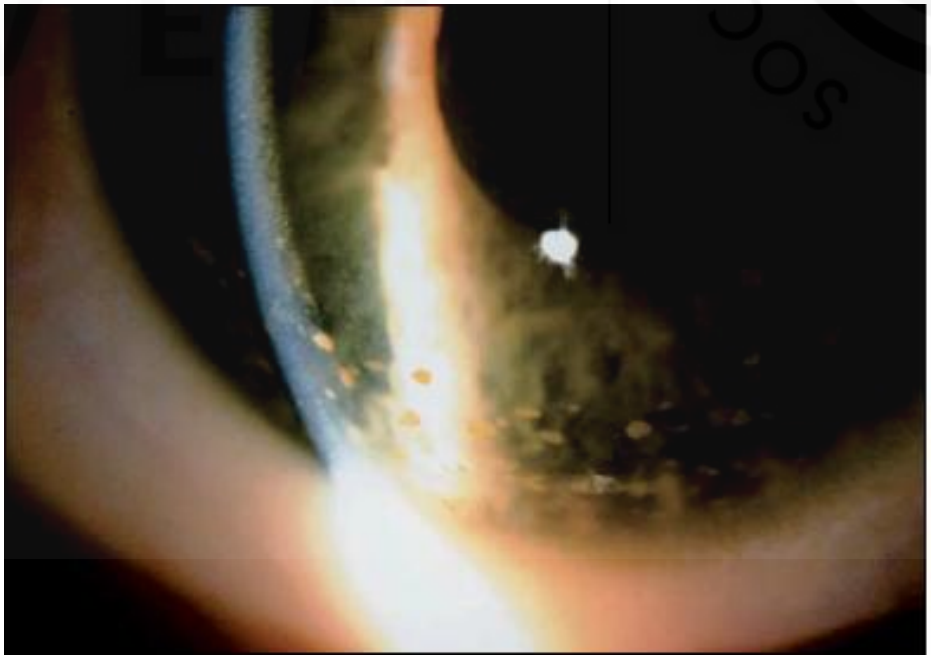




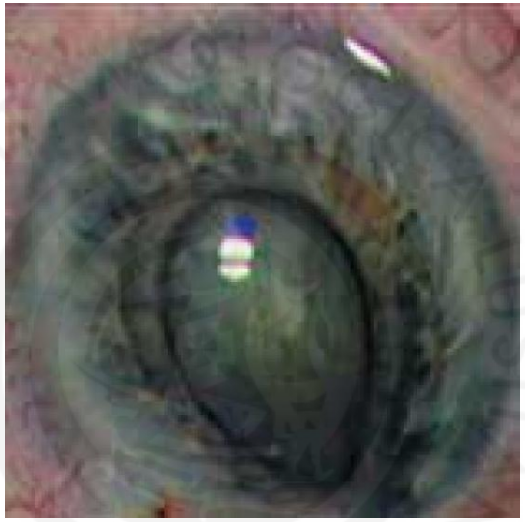
Córnea- endotélio

- Depósitos pigmentados

  - Rifabutina: *Mycobacterium avium*, *Mycobacterium tuberculosis*



Floppy-iris syndrome



- Fármacos α1-antagonistas

  - HBP

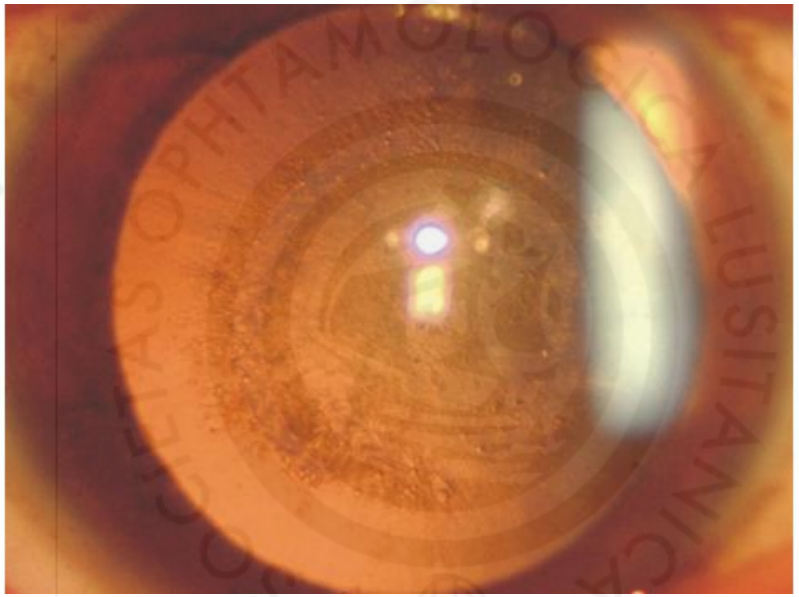
  - tansulosina, alfuzosina, doxasozina, terazosina

  - receptores α1A: diminuição do tónus do músculo dilatador da íris

  - dose, duração, susceptibilidade individual

  - sem necessidade de suspender fármaco

Cristalino



- Corticóides

  - tópicos e sistémicos

  - catarata SCP

  - depende da dose e da duração

  - menos de 4 anos ou menos de 10 mg/dia prednisolona?

  - pode ser reversível

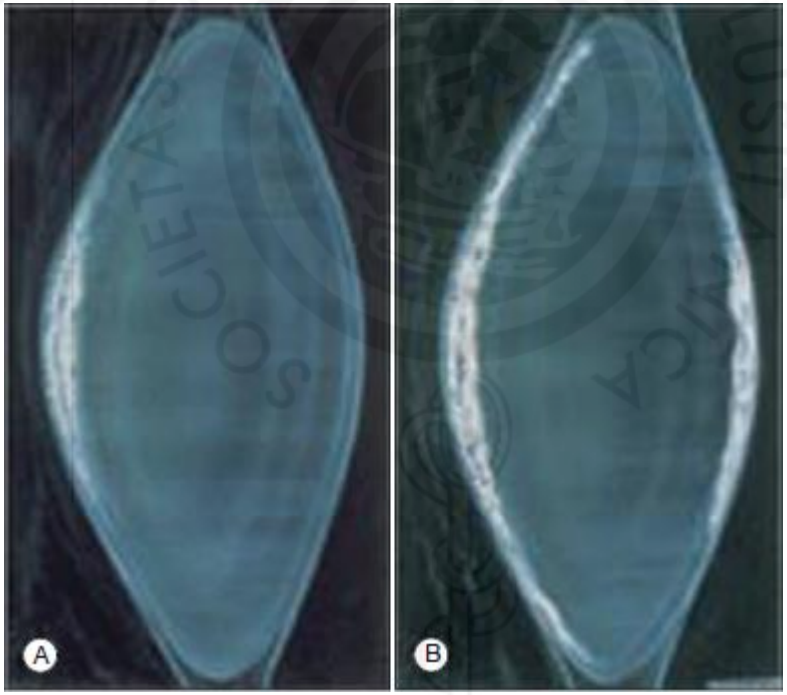
Cristalino

- Corticóides

  - proliferação de células epiteliais

  - inibição de apoptose

  - ERO



Cristalino

- Corticóides

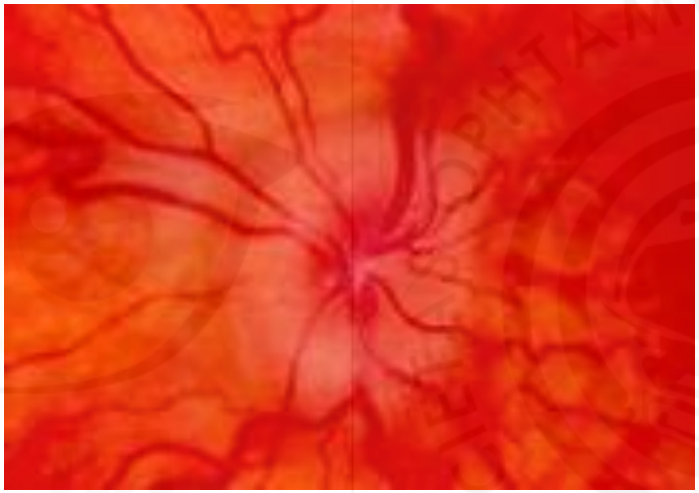
  - HTO

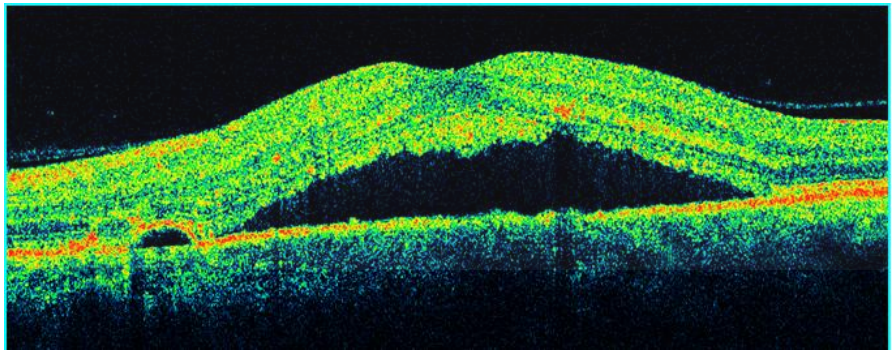
  - HIC

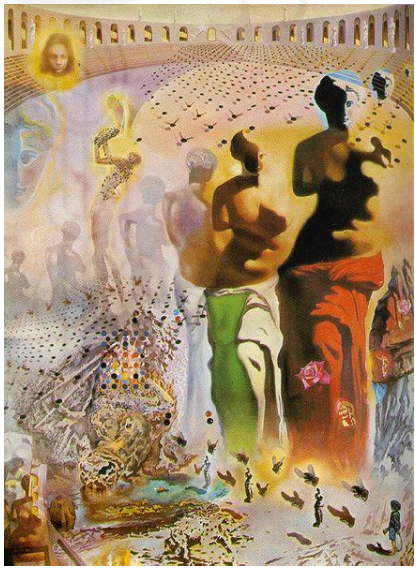
  - CRSC

  - alucinações visuais

  - ...







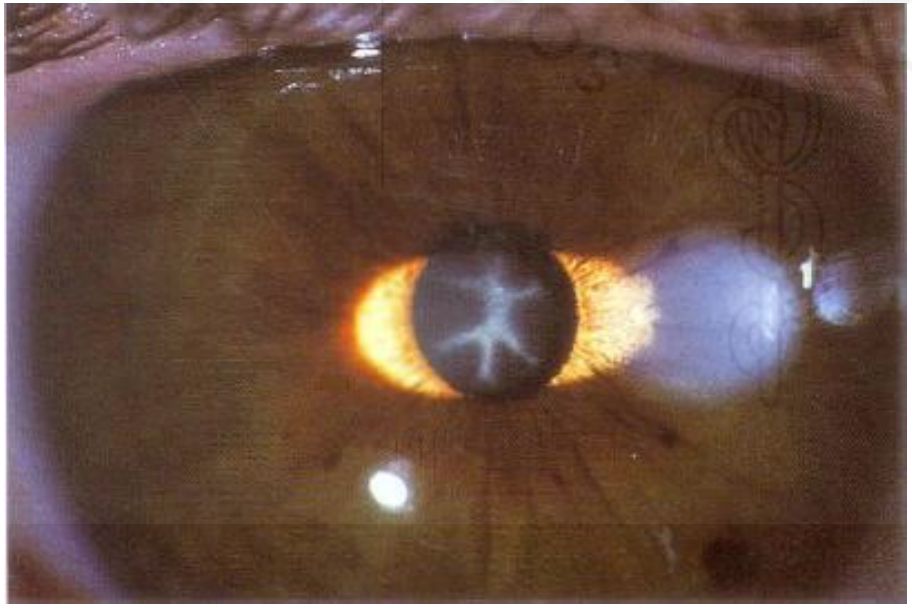
Cristalino

- Fenotiazinas

  - clorpromazina, tioridazina

  - depósitos finos, estrelados; inócuos

  - dose > 1000 g



Glaucoma ângulo aberto

- Corticóides

  - tópicos e sistémicos

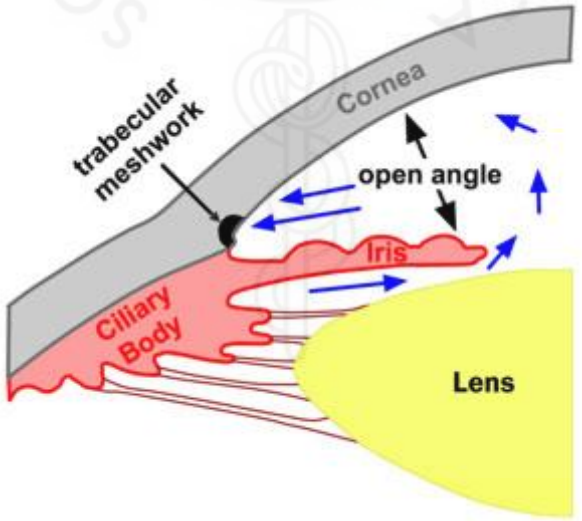
  - remodelação estrutural e funcional da malha trabecular

  - dose, duração, susceptibilidade individual

  - correlação entre catarata e HTO

- Anti-neoplásicos

  - docetaxel e paclitaxel



Glaucoma ângulo fechado

- Agonistas adrenérgicos

  - adrenalina, efedrina

  - salbutamol

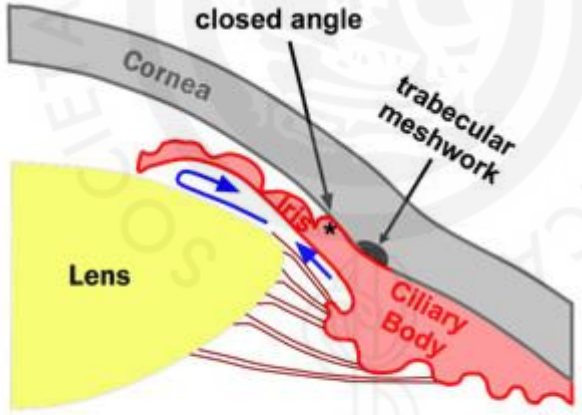
- Anticolinérgicos

  - brometo de ipatrópio

  - fluoxetina, paroxetina, venlafaxina

  - cimetidina, ranitidina

- Topiramato

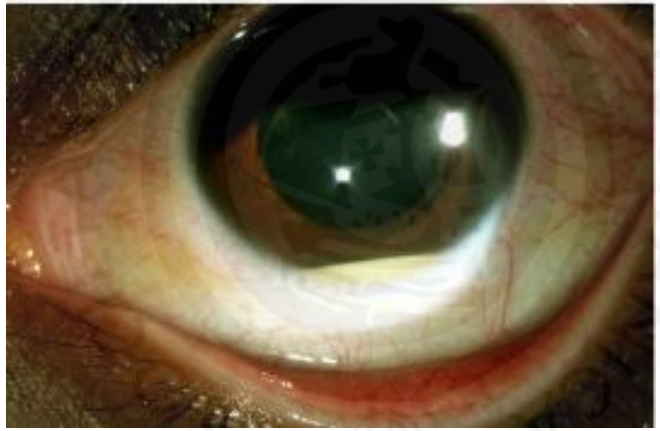


Uveíte

- Rifabutina

  - uveíte anterior, hipópion, vitrite

  - suspensão ou redução da dose



- Cidofovir

  - CMV em doentes VIH+

  - EV, intra-vítrea

  - uveíte anterior, hipópion, vitrite; hipotonia

  - suspensão da Tx

Uveíte

- Bifosfonatos

  - risedronato, pamidronato

  - uveíte anterior

- Sulfonamidas

  - trimetoprim-sulfametoxazol

  - uveíte anterior, bilateral

- Contraceptivos orais

  - uveíte anterior, uveíte posterior, vasculite

Retina

- Antimaláricos

  - melanotrópicos: EPR

Duration of use	>5 yrs
Cumulative dose	
HCQ	>1000 g (total)
CQ	>460 g (total)
Daily dose	
HCQ	>400 mg/day (>6.5 mg/kg ideal body weight for short individuals)
CQ	>250 mg/day (>3.0 mg/kg ideal body weight for short individuals)
Age	Elderly
Systemic disease	Kidney or liver dysfunction
Ocular disease	Retinal disease or maculopathy

CQ = chloroquine; HCQ = hydroxychloroquine.

Marmor MF et al. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. Ophthalmology 2011 Feb; 118:415.

Retina

- Antimaláricos

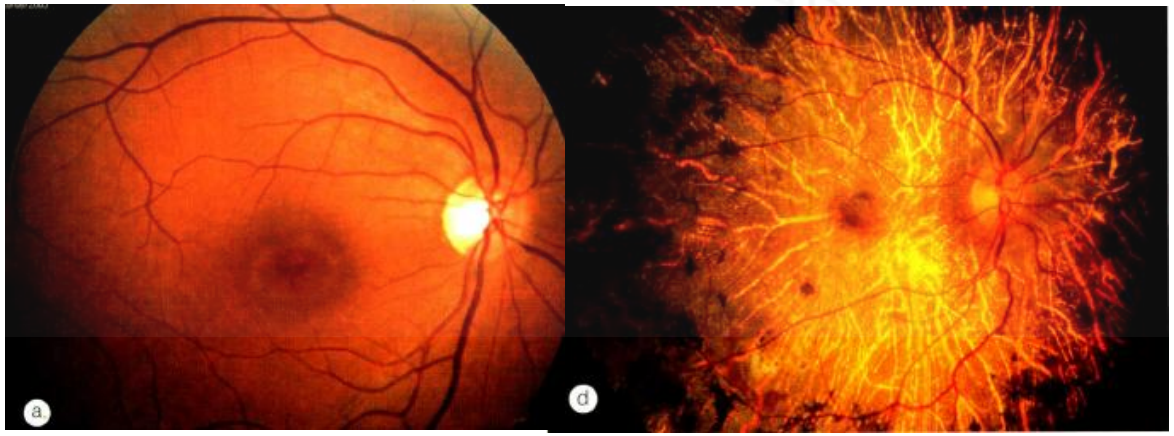
  - escotoma para-central, diminuição da AV, perda de visão periférica, nictalopia

  - despigmentação granular para-foveolar

  - maculopatia em "olho de boi"

  - despigmentação de toda a retina

  - irreversível

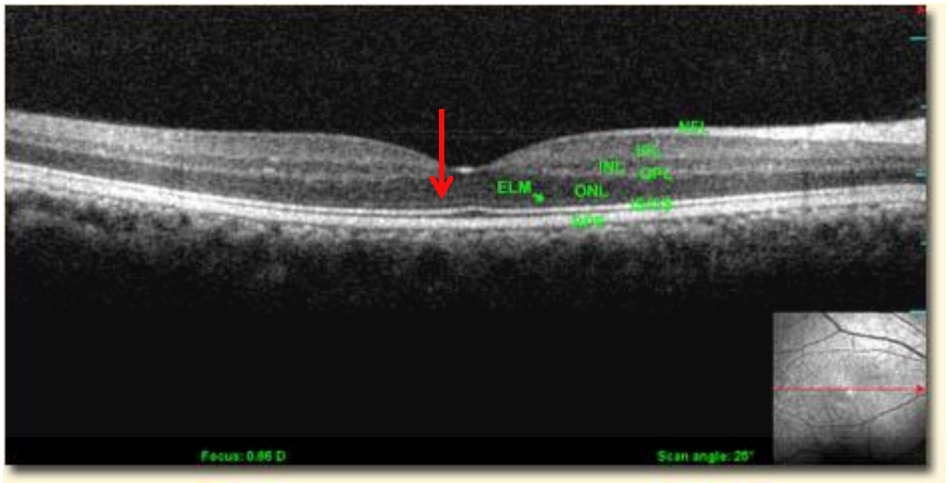


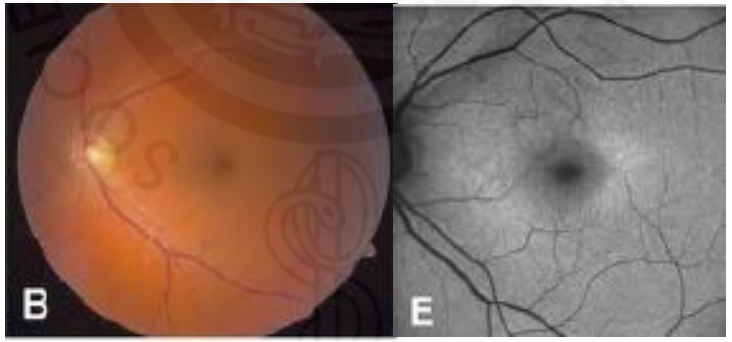
Retina

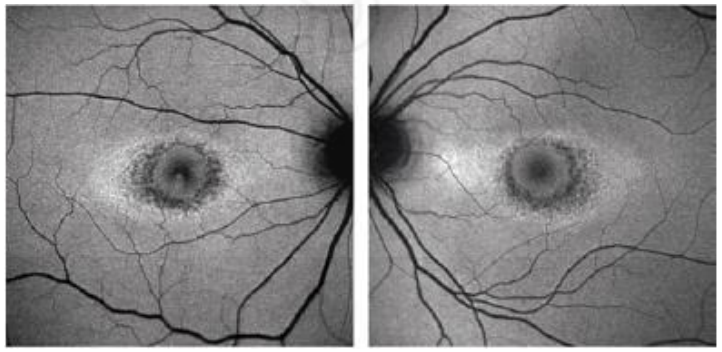
- Antimaláricos

  - avaliação basal: exame oftalmológico, retinografia, PEC 10º centrais e, se possível, OCT-SD, FAF e/ou ERG multifocal

  - avaliação anual a partir dos 5 anos







Retina

- Vigabatrina

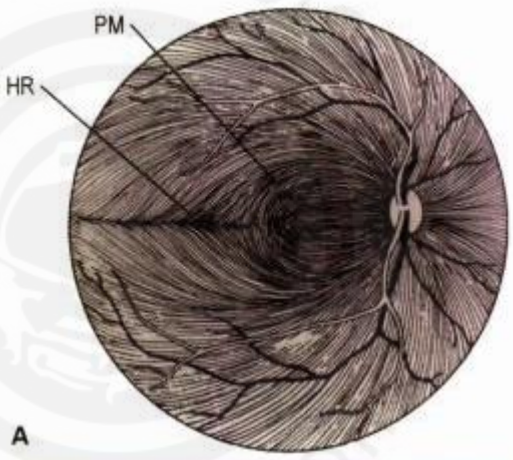
  - epilepsia refractária do adulto e espasmos infantis

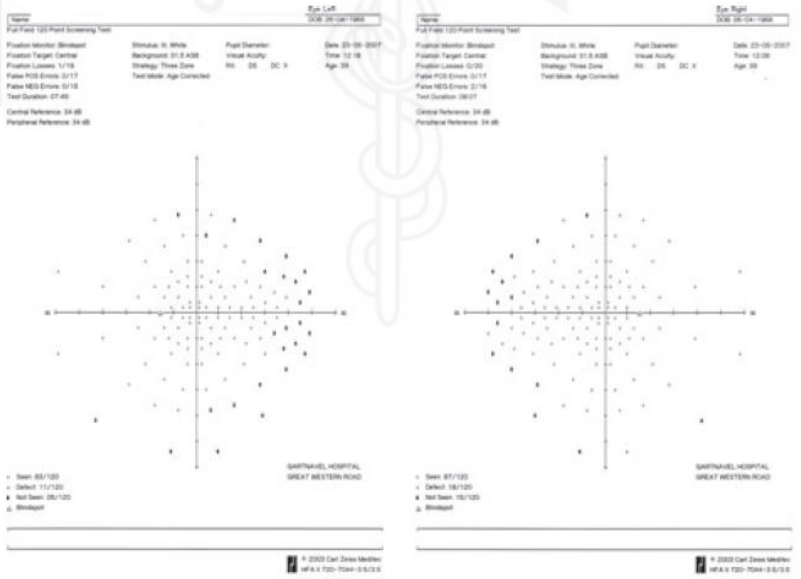
  - dose dependente? Idiossincrático?

  - constrição periférica concêntrica, bilateral

  - “atrofia óptica inversa”

  - irreversível





Plant G, Sergott R. Understanding and interpreting vision safety issues with vigabatrin therapy. Acta Neurol Scand 2011: 124 (Suppl. 192) 57–71

Retina

- Vigabatrina

  - avaliação até 4 semanas após início; *follow-up* a cada 3 meses

  - PEC

  - ERG *full-field*

  - OCT (?)

Table 1 Suggested visual function evaluations by developmental age and/or ability to be performed by ophthalmologists

	Developmental age and/or ability				
Type of evaluation	Infants ≤2 years	2–9 years	>9–12 years	>12 years	Patients unable to perform reliable perimetry
History of visually oriented behavior	Ask parents				Ask family
Complete ophthalmologic examination	Pediatric examination, including dilated funduscopy	Pediatric examination		Standard examination	
Confrontation testing*	Present toys or other objects of interest			Standard test	
Perimetry testing	Not recommended		Attempt automated static or kinetic (SSA) perimetry or Esterman binocular test with both eyes open†; If unable, arrange for Goldmann kinetic perimetry		Not reliable
Electrophysiologic testing or imaging			Full-field ERG		
	OCT not recommended	OCT† (children age 6–8 years may be able to do OCT)		OCT†	

ERG, electroretinography; OCT, optical coherence tomography; SSA, Social Security Administration.
* Cognitive ability should be taken into consideration.
† Exploratory test.

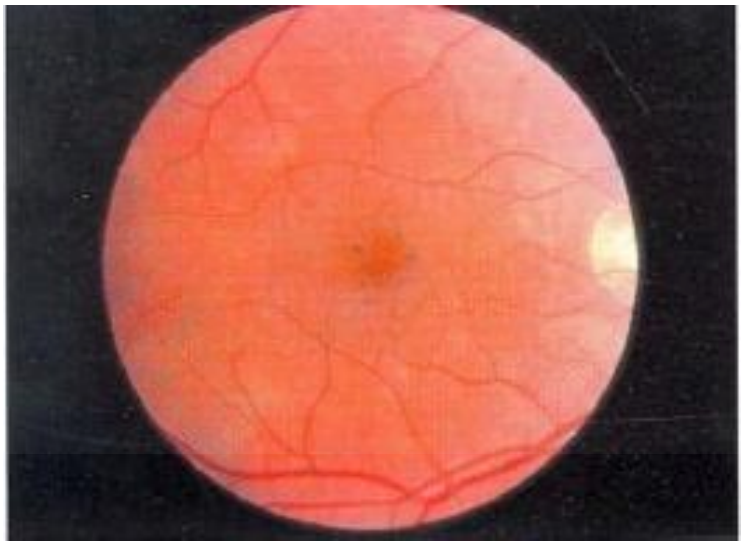
Sergott R. Recommendations for visual evaluations of patients treated with vigabatrin. Current Opinion in Ophthalmology 2010, 21:442–446

Retina

- Fenotiazinas

  - tioridazina: > 800 mg/dia

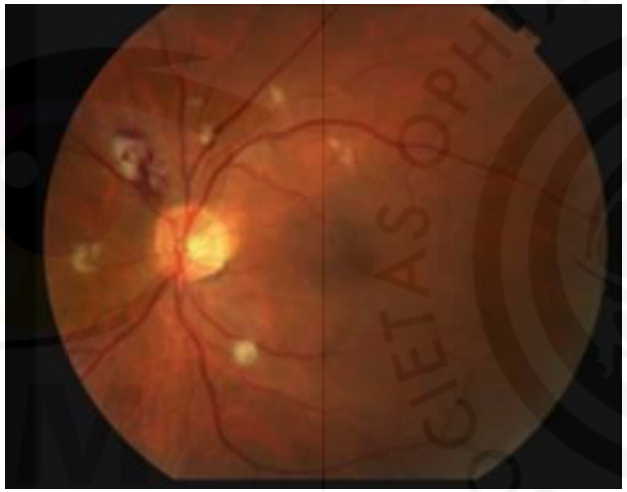
  - clorpromazina: > 300 mg/dia





Retina

- Interferão alfa
- Digitálicos
- Isotretinoína





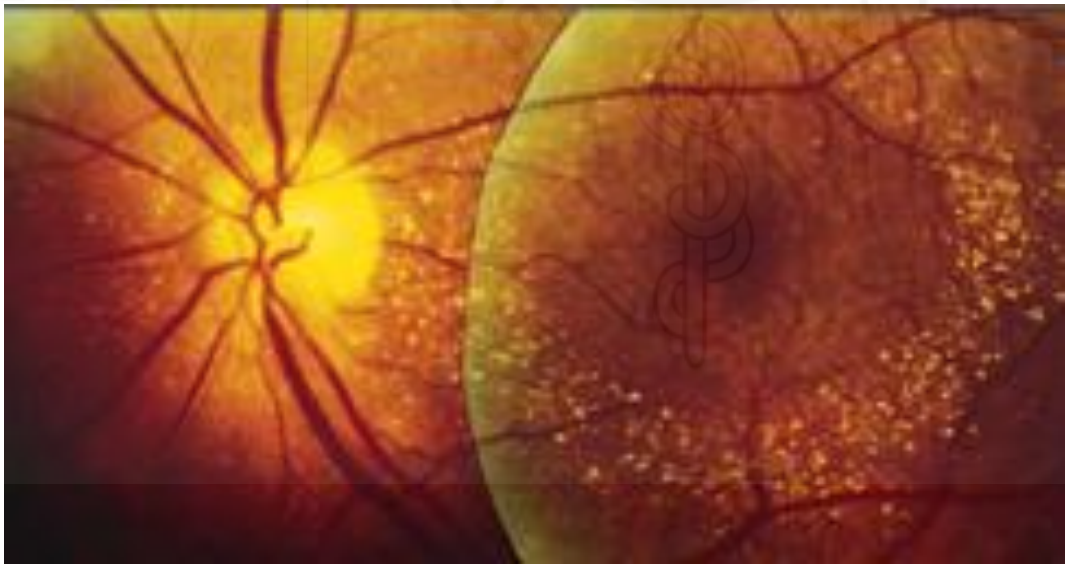
Retina

- Maculopatia cristalina

  - Tamoxifeno

  - Nitrofurantoína





Nervo óptico

- Etambutol

  - neuropatia óptica insidiosa, sub-aguda ou aguda

  - disfunção mitocondrial?

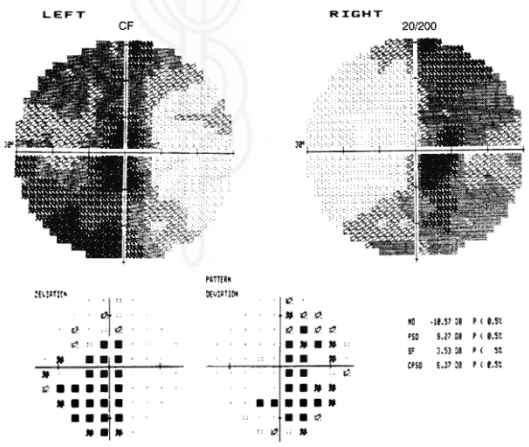
  - rara se < 15 mg/kg/dia, 5-6% se >25 mg/kg/dia

  - escotoma central, defeito bitemporal,

    constrição periférica

  - avaliação basal: AV e visão cromática, PEC(?)

  - prognóstico variável



Nervo óptico

- Isoniazida

  - neuropatia óptica por défice de piridoxina (B6)?

  - parar isoniazida se ausência de melhoria 6 semanas após suspensão de etambutol

Nervo óptico

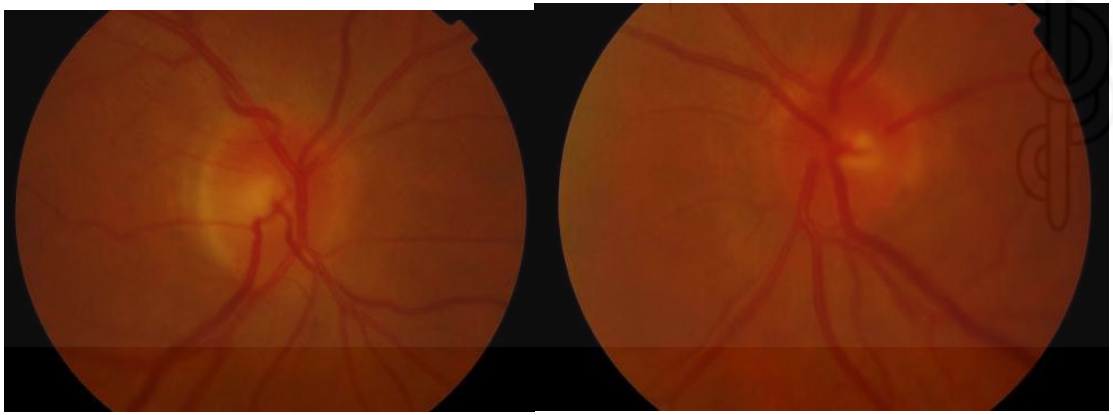
- Cloranfenicol

  - neuropatia óptica, sub-aguda

  - dose > 100 g, duração > 6 semanas

  - suspensão do fármaco, administração de vitamina B6 e B12

  - prognóstico variável



Nervo óptico

- Neuropatia óptica mitocondrial induzida por fármacos

  - etambutol (Leber)

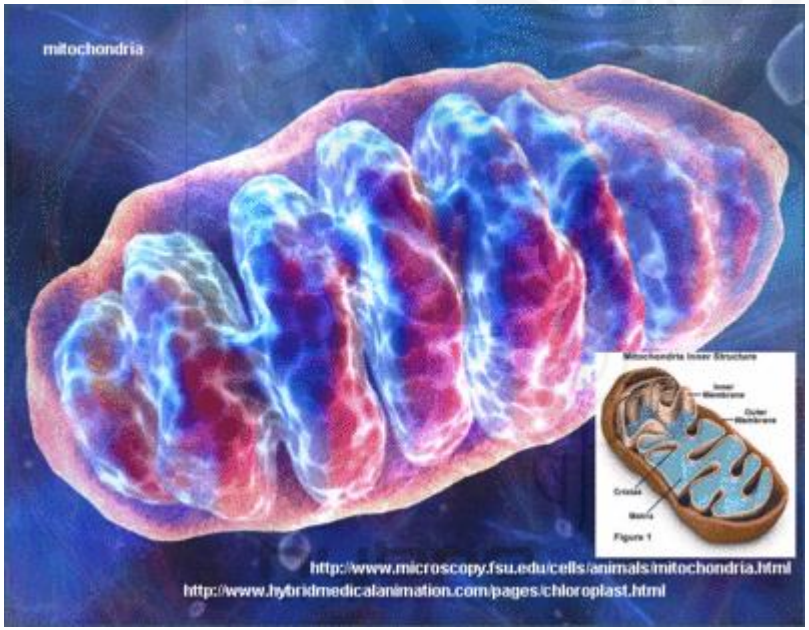
  - cloranfenicol (Leber)

  - linezolide

  - eritromicina

  - estreptomicina

  - anti-retrovirais



Nervo óptico

- Amiodarona

  - NOIA não arterítica (?)

  - instalação insidiosa, bilateral

  - edema do disco persistente

TABLE 6.3. A comparison of neuro-ophthalmic features between NAION and amiodarone-related optic neuropathy (adapted from Johnson et al.[67])

Features	NAION	Amiodarone optic neuropathy
Medication use	Absent	Within 12 months of initiating amiodarone (median, 4 months)
Gender preference	Male same as female	Male more often than female
Incidence	2.3 to 10.2 per 100,000 and more than 50 years of age	About 2% in patients treated with amiodarone
Ocular laterality at presentation	Unilateral	65% bilateral and 35% unilateral
Visual acuity on presentation	20/20 to no light perception	20/20 to 20/200
Optic nerve cup-to-disc ratio	Small (less than 0.2) cup-to-disc ratio	Any cup-to-disc ratio
Increased intracranial pressure	Absent	Occasional
Duration of disc edema after NAION attack/after drug withdrawal	2 to 4 weeks	1 to 8 months (median, 3 months)

Optic Nerve Disorders: Diagnosis and Management. Jane W. Chan

Nervo óptico

TABLE 6.1. Drugs, nutritional deficiencies, and toxins associated with toxic optic neuropathy (adapted from Miller and Newman[5])

Drugs

Antimicrobials: chloramphenicol, chloroquine, clioquinol, dapsone, ethambutol, iodochlorhydroxyquinoline, isoniazide, linezolid, streptomycin

Immunomodulators/immunosuppressives: cyclosporine, interferon-alpha, tacrolimus (FK506)

Chemotherapeutics: carboplatin, chlorambucil, cisplatin, 5-fluorouracil, methotrexate, nitrosureas (BCNU, CCNU, ACNU), paclitaxel, tamoxifen, 5-vincristine, cytosine arabinoside, purine analogues, procarbazine, cyclophosphamide, vinca alkaloids

Other drugs: amiodarone, amantidine amoproxen, cafergot, chlorpropamide, cimetidine, clomiphene citrate, deferoxamine, disulfiram, emetine, infliximab, pheniprazine, quinine, sildenafil

Obrigado pela atenção!