

OPHTHALMIC USES OF ATROPINE: A REVIEW

Abstract

Atropine has been used in medical practice for decades and is one of the essential emergency drugs. Its applications in ophthalmology has also followed a long trajectory. Therefore, this review is intended to explore the various uses of Atropine in ophthalmology. Atropine uses in strict ophthalmic indications have extensive diagnostic and therapeutic outlay including Examination under anesthesia, cycloplegic refraction, myopia and amblyopic management, post trabeculectomy management, synechiae treatment, floppy iris syndrome and uveitis management. The side effects have been shown to be dose dependent with no long-term sequelae. Atropine has remained an important medicine in ophthalmic practice globally.

Keywords: Atropine, ophthalmic, uses

Introduction

Atropine occurs as a tertiary amine (alkaloid) extracted from a perennial bushy herb known as “deadly nightshade” (Atropa belladonna)¹ Belladonna is an Italian word which means beautiful lady, owing to the historical uses of its extract by women to dilate their pupils.² Atropine is also derived from plants of the Solanaceae family. It has a broad spectrum of central and peripheral actions, and principally causes mydriasis and cycloplegia in the eyes, while the systemic effects

2-5 hours. Its ocular effects last for days. Hepatic oxidation is responsible for its partial metabolism while about 30-50% is excreted unchanged in the urine.^{1,6} This review aims to highlight the different ocular uses of atropine from existing literature.

Atropine has a wide range of therapeutic indications; in surgery, it can be used for anesthetic premedication owing to its ability to reduce salivary secretions and prevent bradycardia prior to intubation.⁷ Also, during surgery, its anti-vagal properties help to prevent attendant cholinergic effects and it reverses muscle relaxation effects of many medications. Atropine is a known antidote to anticholinesterase poisoning from ingestion of toxic agents such as muscarinic containing mushrooms, organophosphates, and carbamates.⁸ Its antispasmodic functions serve in the treatment of diarrhea, irritable bowel syndrome, non-ulcer dyspepsia, and diverticular disease, and in the absence of any reversible cause of bradycardia, it is the drug of choice.^{8,9}

All these indications have made atropine retain its place in the list of emergency drugs that should be in any standard resuscitation box.

Systemic adverse effect affects different body systems from the Cardiovascular system (tachycardia, palpitations), GIT (dry mouth, constipation), and Skin (anhidrosis, flushing).^{8,9} Centrally, effects include altered sensorium, hallucinations, irritability, and delirium-like states. All these effects are dose related. However, atropine is contraindicated in people with hypersensitivity states.

Ocular Pharmacology

As with other parts of the body, atropine has also found used in the eyes. The human eye has all 5 muscarinic (M) receptors. These receptor subtypes are located in ocular structures at various

proportions. As a result, a particular subtype of m-receptors predominates in a certain structure. In the human **lens**, the M₁-receptors account for about 88.1% of total M-receptors.¹⁰ In the **conjunctiva**, M₂ and M₃ receptors are predominantly involved in the muscarinic action of goblet cells that contribute to the tear film.¹¹ In the **Iris**, M₃ receptors are mainly responsible for the contraction of the sphincter when stimulated and they account for 75.5% of the M-receptor population.¹⁰ Other receptor groups are M₁ (11.8%), M₄ (10.4%), M₅ (0.4%) and M₂ (undetected). Also, the **ciliary body** whose circular muscle fibers are responsible for accommodative changes has predominantly M₃ receptors (73.5%). Other populations are M₂ (5.4%), M₄ (4.9%), M₅ (2.4%), and M₁ (0.8%).^{11,12}

The competitive binding of atropine to the M-receptors is mainly through the M₃ receptor subpopulation. Thus, preventing contraction of the iris sphincter and circular muscles of the ciliary body.

Ocular uses:

1. **Clinical Examination** –

- i. Cycloplegic refraction (wet retinoscopy) – the use of atropine to induce cycloplegia (a phenomenon in which mydriasis is achieved by paralyzing accommodation through ciliary muscle due to competitive inhibition of the M-receptors, mainly M₃ of the ciliary body). Atropine induced cycloplegia has been explored in cycloplegic refraction where the refractive status of the eye is determined objectively with accommodative action completely paralyzed. Indications include proper estimation of refractive errors in children who may not be able to co-operate properly due to excess accommodation and inability to obey

instructions. Also, in hyperopic adults due to excess accommodation and proper refraction in children who have accommodative esotropia.

ii. Ocular examination under anesthesia (EUA) – this is a common ophthalmic operating room procedure done when full ocular examination in the clinic is precluded due to the patient's age (especially children), level of cooperation, or developmental level. The anesthesia used in this procedure is usually general. Mahmoud et al¹³ in Ilorin, Nigeria reported congenital glaucoma (51.3%), congenital cataracts (12.8%), exotropia, microphthalmia, and megalocornea to be the most common indications for EUA in pediatric age groups. However, another single hospital study by Yip et al¹⁴ showed a nearly different range of indications with tuberous sclerosis complex (20%), neuro-ophthalmic causes, and neurofibromatosis (10.7%) each strabismus being the commonest indications.

Another common indication of EUA not mentioned above is retinoblastoma (RB) which is the most common primary intraocular malignancy of childhood. An experience in Moorefield's Hospital, London has shown RB to be a common indication of EUA which could be multiple in the course of the therapy cycles.¹⁵

2. **Control of myopia** – myopia is considered to be the most common ocular disorder.¹⁶ It is a form of refractive error in which images of light rays form in front of the retina thus causing blurred vision and is easily treated with a minus lens (spectacle or contact lens) or keratorefractive surgery without any serious cause for worry in the simple type. However, high myopia as defined by WHO (Myopia of -5 Diopters or greater) is associated with degenerated

ocular changes.¹⁷ It is often referred to as degenerative or pathological myopia. Eyes with such changes are at a higher risk of developing complications such as retinal detachment, choroidal neovascularization, macular degeneration, foveoschisis, glaucoma, and cataract.^{18,19} Recent studies have shown an alarming increase in the global prevalence of myopia, especially among young people adults in South-East Asia (80-90%) with it being the leading cause of blindness in that area.²⁰ A high prevalence and incidence of myopia in younger age groups are likely to result in a high burden and severity if it progresses to high myopia. The prevalence of childhood myopia varies with age and location but ranges from 1.2% in Nepal to 78.4% in China.²¹⁻³⁰ The lifestyle modification of children especially during the periods of movement restriction occasioned by the COVID-19 pandemic has caused a 1.72 folds increase in a study that observed two cohorts (COVID and Pre-COVID cohort).³¹

Several studies have shown that the use of atropine in varying doses slows down the progression of myopia in children.³²⁻³⁴ The primary effect of atropine appeared to be by slowing the growth of vitreous chamber depth, which in turn decelerates axial length increase.³⁵ Atropine has been incorporated into clinical practice, especially in Asia.¹⁹

3. Management of Amblyopia

Amblyopia is defined as diminished vision as a result of an insult to the visual system during the critical period of development.³⁶ It is usually bilateral but can be unilateral depending on if the level of diminution of vision is out of proportion with the level expected of the underlying ocular pathology (e.g., high refractive error, anisometropia, strabismus or stimulus deprivation) which interferes with the normal cortical development). It is a fairly common condition and affects about 3-5% of children.³⁶

Penalization is a pharmacological or optical process of inducing blurred vision in the better eye to help stimulate the amblyopic eye to function in response to visual stimulus. Atropine is the most common pharmacological agent used for penalization which may be a daily or weekend regimen, depending on parental preference and the practitioner's experience.³⁶ Evidence from a randomized trial of atropine regimens for treatment of moderate and severe amblyopia by the Paediatric Eye Disease Investigator Group shows that results with weekend dosing were similar to the daily option.³⁷

4. Relief of Accommodative Spasm in closed globe injury and keratitis

Accommodative spasm is also known as accommodative excess, hyper accommodation, or ciliary spasm.³⁸⁻³⁹ It is a result of involuntary and prolonged contraction of the ciliary muscle.⁴⁰⁻⁴¹ Causes could be ocular or systemic. Ocular causes include uncorrected hyperopia, prolonged near work, cholinergic drugs, uveitis, closed globe injury, and cornea ulcer. While some systemic causes include emotional stress, head injury, meningitis, migraine, and myasthenia gravis.^{40,42} It is usually characterized by blurry vision eye pain, ocular discomfort, diplopia, headache dizziness, miosis, and excessive convergence.⁴³⁻⁴⁵ Atropine serves as an adjunct to relieve the spasm while the primary cause is being investigated and treated.

In microbial keratitis, the ability of atropine to relieve pain and prevent synechiae formation by mydriasis is beneficial and in clinical use. Topical 1% preparation also has antimicrobial effects that supplement the primary antimicrobial therapy used in keratitis.^{46,47}

5. Adjunct in treatment of anterior uveitis

Uveitis is the inflammation of the middle layer (tunic or coat) of the eye.⁴⁸ It is a challenging and potentially blinding condition. It is an important cause of visual impairment and negative vision-related quality of life worldwide and affects both developed and developing countries, though with varying outcomes.⁴⁸ It is classified based on the part of the uvea affected; anterior (iris-iritis), intermediate (ciliary body – cyclitis), posterior uveitis (choroid – choroiditis or chorioretinitis).

The principle of treatment is to;⁴⁹

- Treat the primary cause
- Relieve symptoms
- Minimize sequelae (e. g. synechiae)
- Prevent irreversible vision loss (e. g. cataract, with synechiae, panuveitis, ciliary shutdown, or retinal detachment)
- Prevent recurrence
- Limit side effects of medications

The cycloplegic property of atropine is applied in relieving pain. The mydriatic property helps prevent synechiae which is a challenging sequela. Prevention of synechiae also prevents the development of complicated cataracts and also the elevation of intraocular pressure which can eventually lead to irreversible visual loss.⁵⁰

6. Breaking of Synechiae

When uveitis is complicated by posterior synechiae, it can predispose to cataract with synechiae from fibrotic membranes, pupil block, and secondary angle closure. Most times, under such conditions, atropine alone will not help as its cycloplegic property only causes ciliary muscle paralysis and mydriasis. Results from unopposed action of the radial muscle fibers,⁵¹ which is insufficient to break the fibrotic membrane.

In the early phase, a combination of steroids, topical application of atropine, and a sympathomimetic (e. g. 2.5% or 10% phenylephrine) are sufficient to break the membrane.

Atropine is also a component of mydriacaine (Numbers 1 and 2). It is a combination of 0.12mg adrenaline, 1mg atropine, and 6mg procaine. It can be administered as a cotton pledget in the fornices. Also, a subconjunctival injection is effective. Any of these application routes is sufficient to break fresh posterior synechiae, however, injections have been associated with cardiovascular events such as sinus tachycardia.⁵²

7. Atropine in Post Trabeculectomy Care

An important application of the cycloplegic and mydriatic effect of atropine is in the deepening of the anterior chamber as a result of flattening and posterior movement of the lens and increasing distance between the ciliary body and the lens following paralysis of the ciliary muscle.⁵²⁻⁵³ Orengo *et al*⁵⁴ in 2000 reported a statistically significant deepening of the central and peripheral anterior chamber in a randomized controlled clinical trial that involved two groups of post trabeculectomy patients in which one group received atropine and the other did not. Atropine may not prevent postoperative complications in routine use after trabeculectomy but has been found to be very useful in a shallow anterior chamber where it helps in deepening it.

One percent atropine is also used in the treatment of malignant glaucoma which is a challenging complication of trabeculectomy.⁵² Atropine is also useful in the management of choroidal effusion and detachment.⁵⁵ Outside trabeculectomy, 1% atropine is used in the medical treatment of pseudoexfoliative glaucoma.⁵⁶

8. Intraoperative Floppy Iris Syndrome (IFIS)

As the name implies, it is an intraoperative complication of cataract surgery due to poor pupillary dilation. It is characterized by flaccid iris stroma in response to intraocular fluid currents, and progressive pupillary constriction with the attendant risk of posterior capsular rupture.⁵⁷ Other potential complications include iris injury, iridodialysis, hyphemia, wound dehiscence, nuclear drop, and wound dehiscence.

It is important to note that miosis of IFIS is characterized by an elastic iris that does not dilate with mechanical stretching compared to other causes of intraoperative miosis like diabetes.⁵⁷ A high index of suspicion is needed to make a diagnosis of IFIS. Of particular note are patients on tamsulosin, finasteride, alfuzosin, doxazosin, prazosin, silodosin, losartan, benzodiazepines, duloxetine and a host of others. Also, antipsychotics like quetiapine, chlorpromazine, zuclopenthixol, aripiprazole, and risperidone.⁵⁸⁻⁶²

In such patients, especially those on alpha-adrenergic agonists for benign prostatic hyperplasia, preoperative pupillary dilation with

Floppy iris syndrome is one example of why extensive atropine is used with or without epinephrine to prevent this unwanted on the operating table.^{8,63,64} There appears to be no

consensus as to the preferred concentration but the use of 1% is common. A review of drug history is important in the preoperative evaluation of cataract patients.

Available ophthalmic preparation of atropine

The different ophthalmic indications may demand different dosages and preparations. Atropine sulfate formulations are commercially available as 0.3%, 0.5%, 1%, and 2% preparations as topical eye drops while the ointment is available as a 1% formulation as shown in the table below.^{8,46,47,52}

Table 1 shows ocular preparations of atropine, indications, and side effects

<i>Preparation</i>	<i>Concentration</i>	<i>Indication</i>	<i>Ocular side effects</i>
<i>Eye drop</i>	0.1%, 0.3%, 0.5%	Myopia	Ocular irritation Contact dermatitis on lid skin Elevation intraocular pressure Risk of angle closure
	1%	Cycloplegia in amblyopia Keratitis Shallow Anterior chamber Cycloplegic refraction Uveitis	
<i>Ointment</i>	2%	Uveitis	
	1%	Ciliary spasm Cycloplegic refraction EUA in pediatric glaucoma, strabismus, retinoblastoma, retinopathy of prematurity, and other causes of leukocoria	
<i>Conjunctival injections and pledgets</i>	Mydriacaine No 1 and 2 (1% atropine, 1mg adrenaline and 6mg procaine)	Posterior synechiae	

Conclusion

Atropine has various diagnostic and therapeutic uses in Ophthalmology. The safety profile is excellent, and the side effects are usually dose-dependent with no long-term sequelae.

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References

1. Hillier K (2007). Atropine. In: S.J. Enna, David B. Bylund (eds). xPharm: The Comprehensive Pharmacology Reference. Elsevier, pp 1-5. ISBN 9780080552323. <https://doi.org/10.1016/B978-008055232-3.61267-X>.
2. Beyer, J (2012). Herbal Psychoactive Substances. 10.1016/B978-0-12-382165-2.00317-2.
3. National Center for Biotechnology Information (2022). PubChem Compound Summary forCID174174,Atropine.RetrievedJune5,2022 from <https://pubchem.ncbi.nlm.nih.gov/compound/Atropine>.
4. Tran HDM, Tran YH, Tran TD, Coroneo M, Sankaridurg P. A review of myopia control with atropine. J Ocul Pharmacol Ther. 2018;34:374–379.
5. McBrien NA, Stell WK, Carr B. How does atropine exert its anti-myopia effects? Ophthalmic. Physiol Opt. 2013;33:373–378.
6. Medscape. Atropine IV/IM (Rx). Available online from <https://reference.medscape.com>. Accessed April 30, 2022.
7. Rachana PB, Sequeira J. Effect of intramuscular atropine sulphate and glycopyrrolate on heart rate and salivary secretion in patients undergoing minor oral surgical procedure. CUREUS. 2020;12(11):e11780.
8. Del Valle IC, Alvarez-Lorenzo C. Atropine in topical formulations for the management of anterior and posterior segment ocular diseases, Expert Opinion on Drug Delivery 2021, 18:9, 1245-1260, DOI: [10.1080/17425247.2021.1909568](https://doi.org/10.1080/17425247.2021.1909568)
9. McLendon K, Preuss CV. Atropine. [Updated 2022 Mar 13]. In: StatPearls [Internet]. Treasure Island (FL):StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK470551>.

10. Collison D.J., Coleman R.A., James R.S., Carey J, Duncan G. Characterization of muscarinic receptors in human lens cells by pharmacologic and molecular techniques. *Invest. Ophthalmol. Vis. Sci.* 2000; 41:2633–2641
11. Mitchelson F. Muscarinic receptor agonists and antagonists: effects on ocular function. *Handb Exp Pharmacol.* 2012;(208):263-98. doi: 10.1007/978-3-642-23274-9_12. PMID: 22222703.
12. Gil DW, Krauss HA, Bogardus AM, Wolde Mussie E. Muscarinic receptor subtypes in human iris-ciliary body measured by immunoprecipitation. *Invest Ophthalmol Vis Sci* 1997; 38:1434–1442
13. Mahmoud AO, Ayanniyi AA, Oyedepo OO. Pediatric ophthalmic indications for examination under anesthesia in Ilorin, Nigeria. *Ann Afr Med.* 2010; 9:181-183
14. Yip IYM, Tacea F, Dodeja R, Pendlebury J, Yeo DCM. Ophthalmology examinations under anesthesia carried out on non-ophthalmology lists in a specialist children's hospital. *Eye* 2022; 36:669-670.
15. Fabian ID, Shah V, Kapelushnik N, *et al.* Examinations under anesthesia as a measure of disease burden in unilateral retinoblastoma: the London experience. *British Journal of Ophthalmology* 2020; 104:17-22.
16. Wu PC, Chuang MN, Choi J, *et al.* Update in myopia and treatment strategy of atropine use in myopia control. *Eye* 2019;33(1):3-13. doi:10.1038/s41433-018-0139-7.
17. World Health Organization. *The impact of myopia and high myopia.* Geneva, Switzerland: WHO; 2016.
18. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res.* 2012; 31:622–660.

19. Ohno-Matsui K, Lai TY, Lai CC, Cheung CM. Updates of pathologic myopia. *Prog Retin Eye Res.* 2016; 52:156–187.
20. Wu PC, Huang HM, Yu HJ, Fang PC, Chen CT. Epidemiology of Myopia. *Asia Pac J Ophthalmol* 2016;5(6):386-393. doi: 10.1097/APO.0000000000000236. PMID: 27898441.
21. Saw SM, Carkeet A, Chia KS, Stone RA, Tan DTH. Component dependent risk factors for ocular parameters in Singapore Chinese children. *Ophthalmology.* 2002; 109:2065–2071.
22. Lin LL, Shih YF, Hsiao CK, Chen GJ. Prevalence of myopia in Taiwanese school children: 1983 to 2000. *Ann Acad Med Singapore.* 2004; 33:27–33.
23. Dirani M, Chan YH, Gazzard G, Hornbeak DM, Leo DW, Selvaraj P et al. Prevalence of refractive error in Singaporean Chinese children: the Strabismus, Amblyopia, and Refractive Error in Young Singaporean Children (STARS) Study. *Invest Ophthalmol Vis Sci.* 2010; 51:1348–1355.
24. Fan DS, Lam DS, Lam RF, Lau JTF, Chong KS, Cheung EYY et al. Prevalence, incidence, and progression of myopia of school children in Hong Kong. *Invest Ophthalmol Vis Sci.* 2004; 45:1071–1075.
25. Yoon KC, Mun GH, Kim SD, Kim SH, Kim CY, Park KH et al. Prevalence of eye diseases in South Korea: data from the Korea National Health and Nutrition Examination Survey 2008–2009. *Korean J Ophthalmol.* 2011; 25:421–433.
26. He M, Zeng J, Liu Y, Xu J, Pokharel GP, Ellwein LB. Refractive error and visual impairment in urban children in southern China. *Invest Ophthalmol Vis Sci.* 2004; 45:793–799.

27. He M, Huang W, Zheng Y, Huang L, Ellwein LB et al. Refractive error and visual impairment in school children in rural southern China. *Ophthalmology*. 2007;114: 374–382.
28. Zhao J, Pan X, Sui R, Munoz SR, Sperduto RD, Ellwein LB et al. Refractive error study in children: results from Shunyi District, China. *Am J Ophthalmol*. 2000; 129:427–435.
29. Dandona R, Dandona L, Srinivas M, Sahare P, Narsaiah S, Munoz SR et al. Refractive error in children in a rural population in India. *Invest Ophthalmol Vis Sci*. 2002; 43:615–622.
30. Murthy GV, Gupta SK, Ellwein LB, Munoz SR, Pokharel GP, Sanga L et al. Refractive error in children in an urban population in New Delhi. *Invest Ophthalmol Vis Sci*. 2002;43: 623–631.
31. Zhang X, Cheung SSL, Chan HN, Zhang Y, Wang YM, Yip BH, et al. Myopia incidence and lifestyle changes among school children during the COVID-19 pandemic: a population-based prospective study. *Br J Ophthalmol*. 2021-319307. doi: 10.1136/bjophthalmol-2021-319307.
32. Shih YF, Chen CH, Chou AC, Ho TC, Lin LL, Hung PT. Effects of different concentrations of atropine on controlling myopia in myopic children. *J Ocul Pharmacol Ther*. 1999;15(1):85–90.
33. Shih YF, Hsiao CK, Chen CJ, Chang CW, Hung PT, Lin LL. An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression. *Acta Ophthalmol Scand*. 2001;79(3):233–236.
34. Chua WH, Balakrishnan V, Chan YH, Tong L, Ling Y, Quah BL. Atropine for the Treatment of Childhood Myopia. *Ophthalmol*. 2006; 113:228–91.

35. Kumaran A, Htoon HM, Tan D, Chia A. Analysis of Changes in Refraction and Biometry of Atropine- and Placebo-Treated Eyes. *Invest Ophthalmol Vis Sci*. 2015;56(9):5650–5.
36. Bakal. Amblyopia. Available online from <https://eyewiki.org/atropine>. Accessed April 30, 2023.
37. Repka MX, Kraker RT, Beck RW, Birch E, Cotter SA, Holmes JM, et al. Pediatric Eye Disease Investigator Group. Treatment of severe amblyopia with weekend atropine: results from 2 randomized clinical trials. *J AAPOS*. 2009 Jun;13(3):258-63. doi: 10.1016/j.jaapos.2009.03.002.
38. Rutstein RP, Marsh-Tootle W. Acquired unilateral visual loss attributed to an accommodative spasm. *Optom Vis Sci* 2001;78(7):492–495.
39. Rutstein RP, Daum KM, Amos JF. Accommodative spasm: a study of 17 cases. *J Am Optom Assoc* 1988;59(7):527.
40. Prerana S, Revathy M. Persistent Accommodative Spasm, *Sci J Med & Vis Res* Foun October 2013; XXXI:43–45.
41. Lindberg L. Spasm of accommodation. *Duodecim*. 2014;130(2):168-73. Finnish. PMID: 24605432
42. Daum KM. Accommodative dysfunction. *Doc Ophthalmol* 1983; 55:117–198.
43. Hussaindeen JR, Mani R, Agarkar S, et al. Acute adult onset comitant esotropia associated with accommodative spasm. *Optom Vis Sci*. 2014; 91(4):46–51.
44. Hyndman J. Spasm of the near reflex: literature review and proposed management strategy. *J Binocul Vis Ocul Motil*. 2018; 68(3):78–86.
45. Lind T, Atkinson S, Marsh JD. Diagnosis of accommodative spasm aided by handheld photoscreener. *J Binocul Vis Ocul Motil*. 2020; 70(1):37–39.

46. Garg P, Rao GN. Corneal ulcer: diagnosis and management. *Community Eye Health*. 1999; 12(30):21–23.
47. Shoshany TN, Michalak S, Staffa SJ, et al. Effect of primary occlusion therapy in asymmetric, bilateral amblyopia. *Am J Ophthalmol*. 2020; 211:87–93.
48. Boyd K. What is Uveitis? American Academy of Ophthalmology. Available online from <https://www.aao.org>. Accessed April 30, 2022.
49. Moura-Coelho N, Proenca RP, Dutra-Medeiros M, O’Keefe GD, Palestine N. for Eyewiki. Treatment of Uveitis. Available online from <https://eyewiki.aao.org>. Accessed April 30, 2022.
50. Babu, Kalpana; Mahendradas, Padmamalini¹, Medical Management of Uveitis – Current Trends, *Indian Journal of Ophthalmology* 2013; 61: 277-283
doi: 10.4103/0301-4738.114099
51. Sokwa J, Kabat AG. Develop a flare for uveitis; in *Review of Optometry*. Available online from. <https://www.reviewofoptometry.com/article/>. Accessed April 30, 2022.
52. Brad Browling (Ed). *Kanski’s Clinical Ophthalmology – A Systemic Approach*. 8th Edition. China; Elsevier; 2016. 403 p.
53. Pons ME, Hughes BA, Choplin NT. Malignant glaucoma treatment and management. Available online from <https://emedicine.com/article/1205609-treatment>. Accessed May 15, 2022.
54. Orenngo-Nania S, El-Harazi SM, Oram O, Feldman RM, Chuang AZ, Gross RL. Effects of atropine on anterior chamber depth and anterior chamber inflammation after primary trabeculectomy. *J Glaucoma*. 2000; 9:303-310.
55. Ku W, Lin Y, Chuang L, Yang K. Choroidal detachment after filtration surgery. *Chang Gung Med J* 2005; 28: 151–158.

56. Petal AS, Salim S, Aref AA, Akkara JD, DelMonte DW, Whigham B, Khawaja MA. Pseudoexfoliative glaucoma. Available online from [https://eyewiki.aao.org/Pseudoexfoliative Glaucoma](https://eyewiki.aao.org/Pseudoexfoliative_Glaucoma). Accessed May 15, 2022.
57. Bruxelas CFP, Portela M, Petal as, DelMonte DW, Baptista MI, Stelzner SK. Inoperative floppy iris syndrome and management of small pupils. Available online from <https://eyewiki.aao.org>. Accessed May 15, 2022.
58. Chang DF, Braga MR, Mamalis N, Masket S; Miller K M, Nichamin LD, et al . ASCRS Cataract Clinical Committee ASCRS White Paper: Clinical review of intraoperative floppy-iris syndrome, *J Cataract Refract Surg* 2008;34:2153-2162 doi: 10.1016/j.jcrs.2008.08.031
59. Chang DF, Campbell JR, Colin J, Schweitzer C; Study Surgeon Group. Prospective masked comparison of intraoperative floppy iris syndrome severity with tamsulosin versus alfuzosin. *Ophthalmology*. 2014; 121:829–834.
60. Ipekci T, Akin Y, Hoscan B, Tunckiran A. Intraoperative floppy iris syndrome associated with silodosin. *Acta Ophthalmol* 2015; 93: e306.
61. Christou CD, Tsinopoulos I, Ziakas N, Tzamalīs A. Intraoperative Floppy Iris Syndrome: Updated Perspectives. *Clin Ophthalmol*. 2020; 14:463-471. Published 2020 Feb 20. doi:10.2147/OPHTH.S221094.
62. Kaczmarek IA, Prost ME, Wasyluk J. Clinical risk factors associated with intraoperative floppy iris syndrome: a prospective study. *Int Ophthalmol*. 2019; 39(3):541-549. doi:10.1007/s10792-018-0840-3.

63. Esen F, Erdagi Bulutu A, Toker E. Efficacy and safety of low-concentration, bisulphite-containing, intracameral epinephrine and topical atropine treatments for the prevention of intraoperative floppy iris syndrome. *Cutan Ocul Toxicol.* 2018; 37(3):286–290.
64. Bendel RE, Phillips MB. Preoperative use of atropine to prevent intraoperative floppy-iris syndrome in patients taking tamsulosin. *J Cataract Refract Surg.* 2006; 32(10):1603–1605.

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