



Pharmacoeconomics of anterior ocular inflammatory disease

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Purpose of review

Anterior ocular inflammatory disease (AOID) affects more than 40% of the U.S. population, which includes ocular allergies, various forms of infectious conjunctivitis, and dry eye diseases (tear film dysfunction). This review evaluates the recent economic costs of AOID treatment.

Recent findings

Rapid advances in pharmacotherapy of the anterior surface of the eye have been made as the expansion of the immunopathophysiology underlying these disorders ranging from the innate Toll-like receptors to the more specific IgE receptors are being unravelled. Even with these advances in AOID immunopathophysiology, progressive new treatments that address inflammatory mediators and their receptors with advancements in the development of ophthalmic remain limited. In 2011, AOID represents 40% of cost associated with ophthalmic drugs focusing on dry eye (31%), anti-infectives (30%), anti-allergics (25%), and anti-inflammatory agents (14%). With rising treatment costs, a need for cost-effective medicines remains to be pursued along with the development of treatment algorithms to maximize the therapeutic outcomes.

Summary

The economic burden of AOID has dramatically increased in recent years, with prescription drug expenditure approaching approximately \$7 billion. There is an increasing need for major investment in this sector to improve outcomes as well as provide more effective alternative treatment modalities to the current options.

Keywords

allergies, conjunctivitis, dry eye disease (DED), ocular allergy, pharmacoeconomics

INTRODUCTION

Anterior ocular inflammatory disease (AOID) of the eye affects more than 40% of the U.S. population, as it includes ocular allergies and dry eye diseases (tear film dysfunction) that are comorbid conditions [1,2] as well as infections that are commonly independent, but increased in patients with tear film dysfunction [3]. Visual impairment because of various eye diseases affects more than half of the U.S. population. It is estimated that nearly 3.5 million Americans over 40 years of age are either blind or have impaired vision because of some eye disorder. Over the last 25 years, there has been increasing interest in the research and development of treatments of the ocular surface disease with the goal of controlling ocular surface inflammation, including allergies [4], DED (tear film abnormalities) [5–7], and infections [8]. Financial investment in this area has been ongoing since the early 1990s, paralleling the U.S. Food and Drug Administration

(FDA) increasing the criteria for the approval of products indicated for allergic conjunctivitis and the growing demand for more effective alternatives to current treatments with the expectation that it would exceed \$2 billion in sales by 2012 and has indeed reached this milestone [9,10].

Untreated conjunctivitis is associated with potentially serious complications that include permanent visual loss. Damage to the visual axis through the cornea (keratopathy) is the most significant complication of conjunctivitis that ranges in severity from the essentially reversible punctate

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KEY POINTS

- Anterior ocular inflammatory disease (AOID) affects over 40% of the U.S. population.
- The economic burden of ocular allergies has dramatically increased in recent years; allergic rhinitis with approximately 14.2% people diagnosed in the USA costs over \$6 billion a year. Prescription medication costs for ocular allergy have increased by approximately 25% per year, with the current U.S. expenditure approaching approximately \$1 billion, excluding over-the-counter use being 10-fold more than the prescription use for AOID.
- In Europe, seasonal allergic conjunctivitis (SAC) costs vary. In the UK, the estimated healthcare costs for an employed person with SAC were estimated at £124 per year, with £46 attributed to medication. A Spanish study found the direct cost of SAC to be €151 per patient, with medication costs totalling €68 with a mean of €48 on six medications.
- The prevalence of clinically diagnosed dry eye disease (DED) ranges from 0.1% in Europe and Japan to 0.5% in the USA, being highest among women and the elderly. The annual direct costs for the various grades of DED range from \$678 (mild) to \$1267 (severe), with the total annual direct costs at \$3.8 billion.
- The global ophthalmic market was estimated to worth \$17.8 billion in 2011. Novartis (Alcon) leads with 28.8% market share, followed by Allergan (14.2%) and Genentech/Hoffman La Roche (9.7%). Over 70% of the market was captured by six manufacturers, generating sales of \$12.6 billion.

epithelial keratopathy to corneal ulceration, perforation, and scarring [11]. The severity and rate of complications can be reduced through earlier diagnosis and appropriate treatment regimen, with the realization that conjunctivitis is ubiquitous in the general population. Therefore, it requires the clinician to be alert to these disorders.

Clinicians in various specialties including primary care, eye care specialists, and allergists are becoming more aware of the ocular surface pathology because of the increasing prevalence and advances in the immunopathophysiology; yet, the armamentarium to treat the most common forms of ocular anterior surface disorders are still limited to the few medications approved by the FDA. The medications targeting various primary mediators that generate the clinical signs and symptoms of the ocular surface have recently been the focus of therapeutic advances to restore proper homeostasis of the ocular surface via manipulation of the innate and adaptive immune mechanisms. This has included the baseline content and changes

of mediators, cytokines, interleukins, Toll-like receptors (TLRs), epithelial barrier, and other tear constituents that nourish and protect the ocular surface [12].

Ocular allergy patients definitely also suffer from other comorbid atopic disorders such as allergic rhinitis, atopic dermatitis, and asthma, whereas patients with dry eye syndromes are generally related to other comorbid conditions that increase the propensity to develop tear film dysfunction that include hormonal changes (e.g. menopausal), cardiovascular disorders (e.g. stroke, cardiac arrhythmias, and ischemic heart disease), autoimmune disorders (e.g. rheumatoid arthritis), and depression [13], although ocular surface infections may be independent of the patients' immune status – that is, infecting a normal healthy surface. However, these three forms of anterior inflammatory disorders are not exclusive and commonly complicate each other [1[■]].

THE ECONOMIC BURDEN OF OCULAR ALLERGY

The economic burden of ocular allergy was originally obscured in the allergic rhinitis literature, but the recent surveys such as Allergies in America have found that 14.2% of the adult U.S. population have been diagnosed with allergic rhinitis, costing more than \$6 billion a year and the majority of these patients have ocular symptoms [14]. Medication use accounts for 25% (~ U.S. \$1.6 billion) of the cost, which does not take into account the specific treatments over the counter and prescriptions for ocular allergy [9], which has been reported to be 10 times more than the prescription market (in bottles) [15]. In 1996, the USA spent \$1.58 billion on prescription medication for allergic rhinitis, whereas in 2005, 60% of \$11.2 (~\$6.72) billion was spent on prescription medications for allergic rhinitis [16,17]. Prescription medication costs attributable to ocular allergy have risen in the USA from \$200 million early in the 21st century and these costs have increased by approximately 25% per year, with the current expenditure in the USA of approximately \$1 billion. The total number of prescriptions for ocular allergy in the USA has increased in parallel with these costs by a rate of 20% per year. In the year 2000, 30% of these prescriptions were written by primary care providers, whereas a further 50% could be attributed to eye care and allergy specialists (41 and 9%, respectively) [9,18].

In a study of seasonal allergic conjunctivitis (SAC) in the public healthcare system (Oxfordshire, UK) and private practice settings in Europe with over 200 patients in each study, the Rhinoconjunctivitis

Quality-of-Life Questionnaire (RQLQ) reflected increased ocular symptoms vs. nasal symptoms (2.47 vs. 2.32; with controls 0.58 vs. 0.37) in the public health system of the UK, while similar results were noted in the private ophthalmological practices of Spain (2.20 vs. 1.63) [19,20]. The estimated healthcare costs in the UK for an employed person with SAC were estimated at £124 per year, of which £46 could be attributed to medication [19]. Interestingly, SAC sufferers were significantly more likely to be unemployed than controls [19]. As SAC is part of the spectrum of atopic disorders, these patients also have increased incidence of comorbid allergic-based disorders, including asthma, rhinitis, atopic dermatitis, perennial allergic conjunctivitis (PAC), food and other allergies. The total mean per-sufferer cost of SAC among the private practice study (€348.50) was higher than the public health observation, which included the public healthcare and private out-of-pocket costs ranging between 64.61 pound sterling for a pensioner and 123.69 pound sterling for a person with SAC in paid employment. The study [20] also revealed a progressive decrease in the symptoms from itching to redness to tearing. The most common treatment was the use of antihistamines, followed by steroids, mast cell stabilizers, decongestants, and NSAIDs.

In another study from Spain, SAC sufferers spent approximately 133 min receiving medical attention vs. 40 min in the UK study (Euro/UK pound/U.S. \$ ~1:1.5:1.21). A subsequent study [20] done by the same group found the direct cost of SAC to be €151 per patient, with drug costs totalling €68 with a mean of €48 on six medications. The associated costs of reduced productivity were higher, totalling €198. Overall, as these two European studies suggest, it appears that SAC may be more of an economic burden than allergic rhinitis.

THE ECONOMIC BURDEN OF DRY EYE DISEASE (DED)

There are increasing data from several studies that suggest that the prevalence of clinically diagnosed DED ranges from 0.1% in Europe and Japan to 0.5% in the USA, being highest among women and the elderly [21].

A Japanese study estimating the annual direct cost of DED patients that included therapeutic interventions (medications and punctal plugs) demonstrated that patients used 32.1 ± 20.8 bottles per year of hyaluronic acid ophthalmic solution, 53.1 ± 42.2 bottles per year of artificial tears, and 33.2 ± 23.2 bottles per year of over-the-counter (OTC) eye drops compared with punctal plugs, 4.1 ± 3.9 plugs per year. The direct annual cost per

patient in 2010 was projected to be U.S. \$323 $\pm$ 219 for drugs, U.S. \$165 $\pm$ 101 for healthcare, and U.S. \$530 $\pm$ 384 for punctal plug placement [21].

A U.S. study analyzed the economic impact of DED based on a decision-analytic model in order to integrate the epidemiology, therapeutic intervention, and economics of the incidence and management of a disease differing in the severity of symptoms and treatment. Bayesian models like this are frequently used in various situations to project the costs or assess the cost efficiency of various interventions. These are commonly then confirmed by taking retrospective data to analyze the model 'fitting' and thus resemble to some degree the reality of clinical care and its natural history. The study assessed the cost of therapeutic interventions that included their adherence rates for ocular lubricants, cyclosporine, punctal plugs, nutritional supplements, professional healthcare visits as well as workplace productivity. The annual direct costs for the various grades of DED was \$678 (mild), \$771 (moderate), and \$1267 (severe), which projected the total annual direct costs of DED at \$3.8 billion. Interestingly, there is an apparent increase in the use of office visits for those patients not using cyclosporine and punctal plugs, especially those with severe forms of DED (even outweighing the cost of punctal plugs). More important than the direct costs was the potential impact on indirect costs for mild (\$12 686), moderate (\$12 569), and severe (\$18 168) dry eye symptoms on annual productivity loss [6]. This had been partially substantiated in another study [7] examining a managed care database assessment of DED.

In a study designed to estimate the annual cost in the management of DED patients by ophthalmologists in Europe that included France, Germany, Italy, Spain, Sweden, and the UK, the prevalence was less than 0.1% in all six countries. The range of total annual healthcare cost being managed by ophthalmologists ranged from U.S. \$0.27 million in France [95% confidence interval (CI) U.S. \$0.20, U.S. \$0.38 million] to U.S. \$1.10 million in the UK (95% CI U.S. \$0.70, U.S. \$1.50 million). This study did not include the cost of OTC therapeutics for the self-treatment of those being provided by the primary care providers [22].

CURRENT THERAPEUTIC OPTIONS

Advances in the pharmacotherapy of the anterior surface of the eye have seen a dramatic increase in recent years, as the conjunctival surface had been recognized as an active immunological target. This subsequently led to progressive new treatments focusing on AOID.

OPHTHALMOLOGICAL ANTI-INFECTIVES

There are a large number of eye infections, caused by a range of pathogens. However, bacterial and viral conjunctivitis forms are the most prevalent, with staphylococci bacteria and adenoviruses the most frequent causes of the inflammatory infection.

Other important eye infections, from a pharmacological perspective, are bacterial infections associated with blepharitis (inflammation of the eyelids) and hordeolum (sty), an infection of the sebaceous glands associated with an eyelash hair follicle. Keratitis (inflammation of the cornea) that includes bacterial, viral, and fungal infections is also significant.

The majority of less-serious ocular surface infections are treated by the clinicians using topical antibacterial and antiviral drugs with varying effectiveness [23]. The newest (third/fourth generation) quinolone antibacterial drugs are the most potent agents available. Aminoglycoside antibacterial drugs, however, are cheaper. More serious infections may require subconjunctival injections or systemic antibacterial treatments.

The ophthalmic anti-infective drug market was worth over \$1.4 billion in 2011 (Fig. 1), with Alcon's Vigamox/Vegamox (moxifloxacin) brand dominating this segment with 25.6% of the ophthalmic anti-infective market share. These fluoroquinolone antibiotic eye drops, marketed under license from Bayer, are used to treat the most common eye infection, bacterial conjunctivitis. Other leading brands on the market include Cravit (levofloxacin, Daiichi Sankyo/J&J), with 11.5% market share.

OCULAR ANTI-ALLERGY

In the USA, ocular allergies are estimated to affect 20–40% of the general population, with SAC the most prevalent form of this disease [4]. The treatment options for allergic conjunctivitis vary. Clinicians often prescribe topical anti-allergic agents such as antihistamines, mast cell stabilizers, or a combination of these to manage the disease. The prescription ocular anti-allergy market was worth around \$1.8 billion and occupied 25% of the anterior surface disorders market in 2011 (Fig. 1), with Alcon (Novartis, Ft Hood, Texas, USA) dominating the market with its Patanol/Pataday (olopatadine hydrochloride solution) franchise.

ANTI-INFLAMMATION

The most common ocular inflammatory disorders not caused by infection include uveitis, chalazion, and scleritis. Uveitis, an autoimmune disease that causes inflammation of the uveal tract (iris, ciliary

body, or choroid), is the most common ocular inflammatory disease. The global prevalence of uveitis is estimated at around 2.5 million patients. Scleritis, inflammation of the sclera and chalazion which involves a gradually enlarging nodule on the eyelid, formed by inflammation and occlusion of the meibomian glands, is less common.

Topical corticosteroids, often combined with an anti-infective, are widely used in ophthalmology for anterior segment inflammation, including the suppression of postoperative inflammation. NSAIDs are sometimes prescribed, but are less commonly used. In 2011, the ocular anti-inflammatory products (corticosteroids, NSAIDs, and anti-inflammatory/anti-infective combinations) market was valued at over \$1.7 billion (Fig. 1).

DRY EYE DISEASE (TEAR FILM DYSFUNCTION)

Dry eye syndrome is a growing problem and the one that also increases with age. The first line of treatment for this condition is generally with OTC artificial tear products. Whereas the OTC market for artificial tears is highly fragmented and competitive, the prescription market has few medicines available, especially to treat severe forms of tear film dysfunction. Nevertheless, this market is now worth around \$2.2 billion (Fig. 1).

KEY OPHTHALMIC PLAYERS

The ophthalmic prescription market has traditionally been dominated by a small number of key players. Novartis is the global leader in the ophthalmic sector, further strengthening its position with acquisition of Alcon in April 2010 (Fig. 2). In 2011, over 70% of the market was captured by six companies: Novartis (28.8%), Allergan (14.2%), Genentech/Hoffman La Roche (9.7%), Pfizer (7.2%), Santen Seiyaku (7.0%), and Bausch & Lomb (4.5%) [24²²]. For the most part, ophthalmic R&D is carried out by these big pharmaceuticals, although smaller companies [ISTA (recently purchased by Bausche & Lomb), Sanju, etc.] and research organizations also play a significant role in preclinical research. Today, many of the technology platforms pertinent to the treatment of ocular diseases are owned by smaller (biotech) companies. This has led to significant interest in mergers and acquisitions from the big pharma.

MARKET OUTLOOK

The overall ophthalmic pharmaceutical market appears to approximate \$17.8 billion a year (Fig. 1) [10²]. The conservative estimate for growth in the

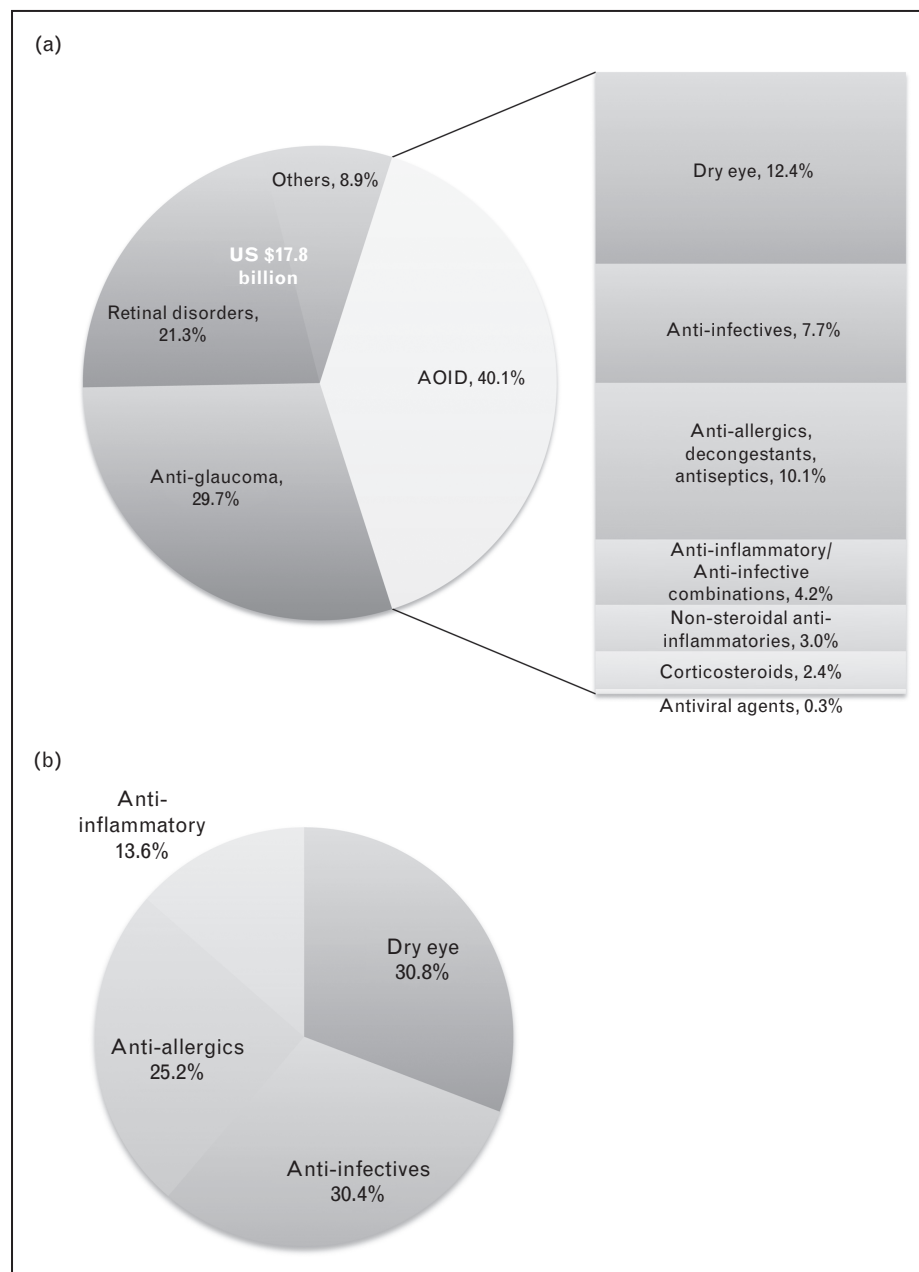


FIGURE 1. (a) Worldwide ophthalmic prescription drugs market in 2011. The anterior ocular inflammatory disease (AOID) drug sales account for approximately 40% of the ophthalmic market. (b) The AOID market had predominantly 'anti-infectives' in the late 1990s, but has since grown to almost equally include anti-allergy (25%), dry eye (31%), and anti-inflammatory agents (14%) as well as the anti-infectives (30%) in 2011.

worldwide overall ophthalmic market is approximately 5% per annum and thus would reach a cost of \$27.5 billion by the year 2020. The anterior surface disorder market comprising ocular allergy, dry eye diseases, and infections presently constitutes 40.1% of the global market, which includes anti-allergy (25%), anti-infectives (30%), dry eye (31%), and anti-inflammatory agents (14%) of the AOID market (Fig. 1b). The initial growth of the ocular allergy market in the USA, one of the fastest growing portions of the U.S. pharmaceutical market for the

first decade of the 21st century, approached 25% per year with sales in 2012 approaching \$2 billion [10¹⁸], excluding OTC medications that was projected to be 10-fold more than the prescription sales in the USA. The other two major ocular domains include glaucoma and retinal disorders because of the increase in aging of the general population and their related ocular disorders. However, it is ocular allergy with the extensive OTC availability that predominates the market share of anterior surface disorders.

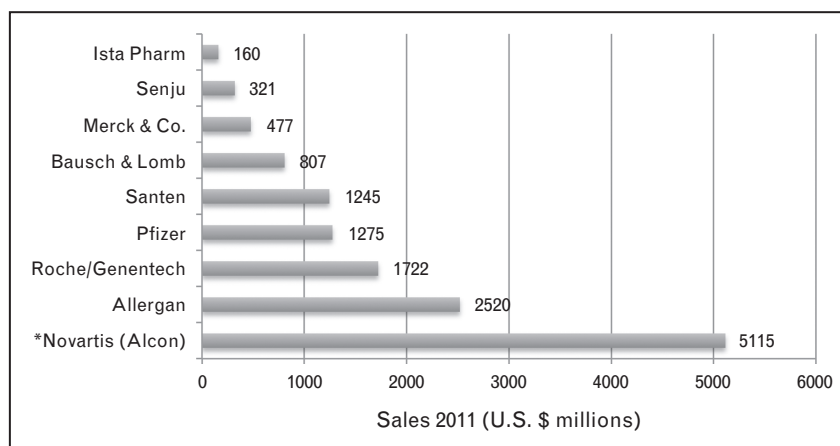


FIGURE 2. Ophthalmic drug sales of the leading companies in the field in 2011. These sales do not include the extensive over-the-counter (OTC) medications for ocular allergy. Novartis acquired Alcon in 2010 and Bausch & Lomb (B&L) completed its acquisition of ISTA Pharmaceuticals in June 2012 (Source: Company reports).

CONCLUSION

The burden of AOID has expanded to include allergic conjunctivitis and DED in addition to infectious conjunctivitis that can cause considerable morbidity leading to direct and indirect financial loss. The primary focus of many of the recent studies has been on their impact on the physiological function of vision, whereas there have been limited clinical studies examining the quality of life (QOL) and economic impact. To date, the limited data available suggest that the new therapeutic interventions have the potential to reduce clinician visits, and that immunotherapy may further improve outcomes with the development of tolerance and the decrease in medications and urgent healthcare visits.

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None.

Conflicts of interest

L.B. is a consultant and has been involved in several clinical research studies supported by Allergan, Bausch & Lomb, Merck, and U.S. Environmental Protection Agency. B.A.S. is employed by Visiongain.

REFERENCES AND RECOMMENDED READING

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 583).

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