Therapeutic Class Overview
Ophthalmic Nonsteroidal Anti-Inflammatory Drugs

Therapeutic Class

- **Overview/Summary:** This review encompasses the ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) bromfenac sodium (Bromday®, Prolensa®), diclofenac sodium, flurbiprofen sodium (Ocufen®), ketorolac tromethamine (Acular®, Acular LS®, Acuvail®) and nepafenac (Ilevro®, Nevanac®).[1-11] These agents are indicated for use prevention of intraoperative miosis during cataract surgery, management of postoperative inflammation, and the reduction of pain and discomfort following cataract and refractive surgery. Although not Food and Drug Administration (FDA)-approved, ophthalmic NSAIDs are also used for the prevention and treatment of cystoid macular edema following cataract surgery.[12,13] Ophthalmic NSAIDs exert their anti-inflammatory activity primarily by nonselective inhibition of cyclooxygenase-1 and cyclooxygenase-2 enzymes.[1-10] Topical administration of anti-inflammatory agents for ocular conditions is preferred over systemic administration due to higher ocular drug concentrations with minimal systemic adverse events.[14-16]

  The American Academy of Ophthalmology and the American Optometric Association both recommend using ophthalmic NSAIDs for preventing and treating cystoid macular edema following cataract surgery. Neither organization recommends one ophthalmic NSAID over another.[17,18] The American Academy of Ophthalmology also recommends the use of NSAIDs in before and after several refractive surgeries.[19] Both organizations note that ophthalmic NSAIDs are effective in treating the signs and symptoms of allergic conjunctivitis.[20,21] The most common adverse events associated with ophthalmic NSAIDs include conjunctival hyperemia, burning and stinging.[15] Corneal ulceration and full-thickness corneal melts associated with the use of these agents is a serious complication. Ophthalmic NSAIDs were first reported to cause corneal melting in 1999. The majority of cases were related to the generic ophthalmic diclofenac sodium solution manufactured by Falcon Laboratories, and ultimately this product was removed from the market. There have been reports of corneal melts and keratitis associated with the use of other ophthalmic NSAIDs; however, available evidence does not alter the favorable benefit-risk ratio of the appropriate use of ophthalmic NSAIDs.[15]

Table 1. Current Medications Available in the Therapeutic Class[1-10]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Bromfenac sodium ophthalmic* (Prolensa®)	Treatment of pain and inflammation associated with cataract surgery	Ophthalmic solution: 0.09% (1.7 mL, 2.5 mL, 5 mL) 0.07% (1.6 mL, 3 mL)	a
Diclofenac sodium ophthalmic	Temporary relief of pain and photophobia in patients undergoing corneal refractive surgery; treatment of postoperative inflammation in patients undergone cataract extraction	Ophthalmic solution: 0.1% (2.5 mL, 5 mL)	a
Flurbiprofen sodium ophthalmic (Ocufen®*)	Inhibition of intraoperative miosis	Ophthalmic solution: 0.03% (2.5 mL)	a
Ketorolac tromethamine ophthalmic (Acular®*†, Acular LS®*†, Acuvail®)	Reduction of ocular pain and burning/stinging following corneal refractive surgery (0.4%); temporary relief of ocular itching due to seasonal allergic conjunctivitis (0.5%); treatment of pain and inflammation associated with cataract surgery (0.45%); treatment of postoperative inflammation in patients who have undergone cataract extraction (0.5%)	Ophthalmic solution: 0.4% (5 mL) 0.45% (0.4 mL single-use vials in package of 30) 0.5% (3 mL, 5 mL, 10 mL)	a

Nepafenac ophthalmic (Ilevro®, Nevanac®)	Treatment of pain and inflammation associated with cataract surgery	Ophthalmic suspension: 0.1% (3 mL) 0.3% (1.7 mL, 3 mL)	-

*Generic available in one dosage form or strength.
† Ketorolac tromethamine 0.5 and 0.4% ophthalmic solutions are available generically.

Evidence-based Medicine

- The ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to be safe and effective in inhibiting intraoperative miosis, reducing postoperative inflammation and pain associated with cataract surgery, relieving pain and photophobia following corneal refractive surgery and relieving seasonal allergic conjunctivitis symptoms in placebo-controlled trials.[22-49,56-64] Although not Food and Drug Administration (FDA)-approved, there is evidence to support the use of ophthalmic NSAIDs for preventing or treating cystoid macular edema and for reducing pain associated with various other refractive surgeries.[51-54]
- The results of head-to-head trials comparing ophthalmic NSAIDs have not consistently demonstrated any one agent to be more efficacious than another for a given indication.[31,32,34,35,48,49,51,52,57,58,61]
- With regard to safety, not one agent was consistently reported to be better tolerated than another across trials, although there is some evidence that the preservative-free products may be associated with less ocular irritation.[45]
- Corneal complications have been reported to occur with all of the agents in the class and the risk does not appear to be higher with one agent vs another.
- Consensus guidelines established by the American Academy of Ophthalmology and the American Optometric Association recommend the use of topical NSAIDs for preventing and treating cystoid macular edema due to cataract surgery. Available evidence suggests that ophthalmic NSAIDs either alone or in combination with ophthalmic corticosteroids are more effective than ophthalmic corticosteroids alone. The ophthalmic NSAIDs are not associated with an increase in intraocular pressure, which may occur with the use of corticosteroids. [17,18]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The use of topical nonsteroidal anti-inflammatory drugs (NSAIDs) for preventing and treating cystoid macular edema due to cataract surgery is recommended.[17,18]
  - For refractive surgery, specifically surface ablation techniques and laser in situ keratomileusis, the use of ophthalmic NSAIDs is recommended. Judicious NSAID application should be done after surface ablation to reduce pain and inflammation and to delay corneal epithelialization NSAID application should be done before laser in situ keratomileusis to ameliorate postop pain. No NSAID is recommended over another.[19]
  - Both organizations note that ophthalmic NSAIDs are effective in treating the signs and symptoms of allergic conjunctivitis.[20,21]
- Other Key Facts:
  - Several formulations are available in generic formulations:
    - Bromfenac 0.09% (twice daily).
    - Diclofenac sodium.
    - Flurbiprofen sodium.
    - ketorolac tromethamine 0.5 and 0.4%.
  - Diclofenac sodium and ketorolac tromethamine 0.45% are the only ophthalmic NSAIDs that are formulated as preservative-free.[4,6]
  - Nepafenac 0.3% and two formulations of bromfenac sodium (Bromday®, Prolensa®) are approved for once daily dosing.[1,2,10]
  - Ketorolac Tromethamine 0.4% is the only ophthalmic NSAID used as needed.[8]

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Therapeutic Class Review
Ophthalmic Nonsteroidal Anti-Inflammatory Drugs

Overview/Summary

This review will focus on the ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs).[1-11] These medications play four principal roles in ophthalmic surgery, including the prevention of intraoperative miosis during cataract surgery, management of postoperative inflammation, the reduction of pain and discomfort following cataract and refractive surgery and prevention and treatment of cystoid macular edema following cataract surgery.[12] Ocular inflammation is a manifestation of cellular and vascular response of the host tissue to injury.[13,14] Tissue injury activates phospholipase A_2, breaking down cell membrane phospholipids to arachidonic acid.[15] Arachidonic acid enters the cyclooxygenase pathway resulting in the formation of prostaglandins and thromboxanes, or enters the lipoxygenase pathway resulting in the formation of eicosanoids.[13,15] Prostaglandins are implicated in the pathogenesis of ocular inflammation. Prostaglandins cause vasodilation and increase vascular permeability resulting in increased aqueous humor protein concentration. They also act on intraocular pressure (IOP) and iris smooth muscle causing miosis.

The pharmacological management of ocular inflammation involves the administration of anti-inflammatory medications.[13] Topical administration of anti-inflammatory agents for ocular conditions is preferred over systemic administration due to higher ocular drug concentrations with minimal systemic adverse events.[13-15] Ophthalmic NSAIDs and corticosteroids are two medication classes used to control and treat ocular inflammation. Ophthalmic corticosteroids have been used in the management of ocular inflammation; however, they are associated with an elevation of IOP and facilitation of ocular infections. Ophthalmic NSAIDs exert their anti-inflammatory activity primarily by nonselective inhibition of cyclooxygenase-1 and cyclooxygenase-2 enzymes.[1-10,16]

The available ophthalmic NSAIDs include bromfenac sodium (Bromday®, Prolensa®, generic), diclofenac sodium, flurbiprofen sodium (Ocufen®), ketorolac tromethamine (Acular®, Acular LS®, Acuvail®) and nepafenac (Ilevro®, Nevanac®).[1-11] The number of drops and duration of therapy with ophthalmic NSAIDs vary depending on drug, and vary further depending on indication and strength.[1-10] Ophthalmic nepafenac 0.3%, bromfenac sodium 0.09% (Bromday® only), and bromfenac sodium 0.07% are approved for once daily dosing.[1,2,10] Ketorolac Tromethamine 0.4% is the only ophthalmic NSAID used as needed.[8] Ophthalmic preparations of bromfenac sodium, ketorolac tromethamine and nepafenac may be used with other product-specific eye drops, but must be administered at least five minutes apart.[1-3,6-10] Ophthalmic formulations of bromfenac sodium 0.09%, diclofenac sodium, flurbiprofen sodium, ketorolac tromethamine 0.5% and 0.4% are available generically. Diclofenac sodium and ketorolac tromethamine 0.45% are the only ophthalmic NSAIDs that are formulated as preservative-free.[1-10]

The American Academy of Ophthalmology and the American Optometric Association both recommend using ophthalmic NSAIDs for preventing and treating cystoid macular edema following cataract surgery. Neither organization recommends one ophthalmic NSAID over another.[17,18] For refractive surgery, specifically surface ablation techniques and laser in situ keratomileusis, the American Academy of Ophthalmology recommends the use of ophthalmic NSAIDs. Judicious NSAID application should be done after surface ablation to reduce pain and inflammation and to delay corneal epithelialization and NSAID application should be done before laser in situ keratomileusis to ameliorate postop pain. No NSAID is recommended over another.[19] Both organizations note that ophthalmic NSAIDs are effective in treating the signs and symptoms of allergic conjunctivitis.[20,21] The most common adverse events associated with ophthalmic NSAIDs include conjunctival hyperemia, burning and stinging.[14] Corneal ulceration and full-thickness corneal melts associated with the use of these agents is a serious complication. Ophthalmic NSAIDs were first reported to cause corneal melting in 1999. The majority of cases were related to the generic ophthalmic diclofenac sodium solution manufactured by Falcon Laboratories, and ultimately this product was removed from the market. There have been reports of corneal melts and keratitis associated with the use of other ophthalmic NSAIDs; however, available evidence does not alter the favorable benefit-risk ratio of the appropriate use of ophthalmic NSAIDs.[14]

Medications

Table 1. Medications Included Within Class Review[1-10]

Generic Name (Trade name)	Medication Class	Generic Availability
Bromfenac sodium ophthalmic* (, Prolensa®)	Nonsteroidal anti-inflammatory drugs	a
Diclofenac sodium ophthalmic	Nonsteroidal anti-inflammatory drugs	a
Flurbiprofen sodium ophthalmic (Ocufen®*)	Nonsteroidal anti-inflammatory drugs	a
Ketorolac tromethamine ophthalmic (Acular®*†, Acular LS®*†, Acuvail®)	Nonsteroidal anti-inflammatory drugs	a
Nepafenac ophthalmic (Ilevro®, Nevanac®)	Nonsteroidal anti-inflammatory drugs	-

*Generic available in one dosage form or strength.
† Ketorolac tromethamine 0.5 and 0.4% ophthalmic solutions are available generically.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-10,16]

Indication	Bromfenac Sodium	Diclofenac Sodium	Flurbiprofen Sodium	Ketorolac Tromethamine	Nepafenac
Inhibition of intraoperative miosis			a		
Reduction of ocular pain and burning/stinging following corneal refractive surgery				a (0.4%)	
Temporary relief of pain and photophobia in patients undergoing corneal refractive surgery		a			
Temporary relief of ocular itching due to seasonal allergic conjunctivitis				a (0.5%)	
Treatment of pain and inflammation associated with/following cataract surgery	a			a (0.45%)	a
Treatment of postoperative inflammation in patients who have undergone cataract extraction		a		a (0.5%)	

In addition to their respective Food and Drug Administration-approved indications, these agents are used off-label for several other ocular procedures and for the treatment and prevention of cystoid macular edema following cataract surgery.[16]

Pharmacokinetics

Due to the topical nature of ophthalmic nonsteroidal anti-inflammatory drugs, limited systemic absorption occurs. After topical instillation, systemic plasma concentration levels of bromfenac sodium and diclofenac sodium remain below the limit of quantification. Systemic absorption of ophthalmic ketorolac 0.4 and 0.45% has not been assessed in humans; however, ophthalmic ketorolac tromethamine 0.5% has been shown to achieve limited systemic plasma concentration. Nepafenac and amfenac steady-state concentrations of 0.310±0.104 and 0.422±0.121 ng/mL respectively, have been observed in majority of patients, two and three hours after ocular administration.[1-10]

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) in their respective Food and Drug Administration (FDA)-approved indications are described in Table 3.[22-64]

The approval of once-daily ophthalmic bromfenac 0.09% (Bromday®) was based on two, randomized, double-blind, placebo-controlled studies in patients requiring cataract surgery. Patients were assigned to receive ophthalmic bromfenac or vehicle (placebo) dosed as one drop per eye starting the day before surgery and continuing for 14 days. The primary endpoint was clearing of ocular inflammation by day 15. The secondary endpoint was the number of patients who were pain-free on day one following cataract surgery. In both studies, once-daily ophthalmic bromfenac was significantly more effective than placebo for clearing inflammation by day 15 (46.1 vs 26.2% and 51.1 vs 27.4% in trials one and two, respectively; P<0.0001 for both comparisons). A significantly higher proportion of patients treated with ophthalmic bromfenac were pain-free on day one following surgery compared to patients treated with placebo (87.0 vs 64.7% and 84.0 vs 67.0% in trials one and two, respectively; P<0.0001 for both comparisons).[22,24] In a study by Donnenfeld et al, a significantly higher proportion of patients randomized to receive ophthalmic bromfenac were cleared of ocular inflammation at day 15 following cataract surgery compared to patients randomized to receive placebo (64.0 vs 43.3%; P<0.0001).[23] . The approval of another once-daily ophthalmic bromfenac 0.07% (Prolensa®) was based on two unpublished multi-center, randomized, double-masked, parallel group and placebo (vehicle)-controlled studies. Patients undergoing cataract surgery self-administered bromfenac 0.07% or vehicle once daily, beginning one day prior to surgery, continuing on the morning of surgery and for 14 days after surgery. The primary efficacy endpoint was the proportion of patients who had complete clearance of ocular inflammation by day 15. In both assessments, complete clearance was observed at a significantly higher proportion of patients in the bromfenac 0.07% group compared to the vehicle at day eight (24.1 vs 6.5%; difference, 17.6%; 95% CI, 8.4 to 26.8 and 30.0 vs 12.7%; difference; 17.3%, 95% CI, 6.7 to 27.9 in trials one and two, respectively). At day 15 inflammation clearance was also significantly higher with bromfenac 0.07% as compared to the vehicle (45.5 vs 13.0%; difference, 32.5%; 95% CI, 21.4 to 43.8 and 45.5 vs 27.3%; difference, 18.2%; 95% CI, 5.7 to 30.7 in trials one and two, respectively). The proportion of patients pain free with bromfenac 0.07% was 81.3 vs 43.5%; difference, 37.7%; 95% CI, 25.9 to 49.6 in the first trial and 76.4 vs 55.5%; difference, 20.9%; 95% CI, 8.7 to 33.1 in the second trial.[2] Another study confirmed these results with 48.6% and 24.3% of the patients in the bromfenac 0.07% and placebo groups, respectively, being cleared of inflammation by day 15 (P<0.0001).[25]

The FDA approval of ophthalmic nepafenac was based on two published, randomized, double-blind, placebo-controlled studies.[27,28] Results of a trial by Lane et al (N=476) demonstrated that a greater number of patients receiving ophthalmic nepafenac 0.1% had an elimination of ocular inflammation compared to patients receiving placebo (P<0.0001).[27] No treatment-related ocular adverse events occurred in either treatment group. In another study by Maxwell et al (N=212), ophthalmic nepafenac 0.1% dosed once daily, twice daily and three times daily for 14 days following cataract surgery significantly reduced the percent of treatment failures, demonstrating effectiveness in resolving ocular inflammation, compared to placebo (P≤0.0029 for all).[28] Fewer patients in the ophthalmic nepafenac 0.1% group experienced adverse events compared to the placebo group. Ophthalmic nepafenac 0.1% was compared to ophthalmic ketorolac 0.4% in combination with different antibiotics (gatifloxacin vs moxifloxacin) and different dosage strengths of ophthalmic prednisolone (1.0 vs 0.125%) following cataract surgery. No differences between the two treatment groups in terms of visual acuity, anterior

chamber inflammation or subjective eye complaints were reported. Patients treated with ophthalmic ketorolac 0.4% reported significantly greater patient satisfaction, patient compliance and postoperative pain control compared to patients receiving ophthalmic nepafenac 0.1% (P=0.022, P=0.023 and P=0.025, respectively). Ophthalmic nepafenac 0.1% was associated with a higher incidence of posterior capsule opacification compared to ophthalmic ketorolac 0.4% (P=0.019).[32]

Ophthalmic diclofenac 0.1% and ophthalmic ketorolac 0.5% instilled four times daily, beginning on the first postoperative day following cataract extraction demonstrated similar anti-inflammatory effects at three postoperative visits and were equally tolerated.[30] In a trial by Koçak et al, ophthalmic diclofenac 0.1% and ophthalmic flurbiprofen 0.03% were not significantly different with regard to conjunctival hyperemia, corneal surface changes, intraocular pressure (IOP) or anterior chamber inflammation.[29] Ophthalmic ketorolac 0.4% and 0.5% were compared in 40 patients undergoing phacoemulsification and intraocular lens implantation.[33] There were no significant differences between the two groups for best-corrected visual acuity, IOP, slit-lamp assessment of cells or cell/flare measured using the laser cell/flare meter. More patients treated with ophthalmic ketorolac 0.5% reported ophthalmic symptoms (foreign body sensation, burning or stinging) one day postoperatively compared to the 0.4% group (P=0.03); however, there were no differences at one week or one month (P values not reported). No adverse events were reported in either treatment group. In another study involving patients undergoing phacoemulsification and intraocular lens implantation, nepafenac 0.3% drops applied daily, nepafenac 0.1% drops applied three times daily, and placebo were compared for clearance of inflammation at 14 days postop. It was found that nepafenac 0.3% daily and nepafenac 0.1% three times a day were non-inferior to each other and superior to placebo (both P<0.001) in terms of clearance of inflammation.[34]

Ophthalmic diclofenac 0.1% was compared to ophthalmic prednisolone 1% and ophthalmic dexamethasone 0.1% with no statistically significant differences being reported at any observation time in terms of postoperative inflammatory reaction between treatments. There was a statistically significant mean decrease from baseline in IOP at week one and month one in the ophthalmic diclofenac 0.1% group compared to the ophthalmic prednisolone 1% group (P=0.007).[32] At one month, the IOP was higher in the ophthalmic dexamethasone 0.1% group than in the ophthalmic diclofenac 0.1% group (P<0.05).[39] Ophthalmic ketorolac 0.5% has been compared to ophthalmic formulations of loteprednol 0.5%, rimexolone 1%, prednisolone 1% and fluorometholone in several clinical trials.[40-45,47] Overall, no significant differences were reported between the treatment groups in measurements of postoperative inflammation or IOP. In a study by Hirneiss et al, there was a difference in overall aqueous flare in the anterior chamber between the treatment groups, lowest being in the ophthalmic ketorolac 0.5% group, followed by the ophthalmic prednisolone 1% and rimexolone 1% groups (P=0.008).[46] Ophthalmic ketorolac 0.5% was associated with a significantly higher IOP value compared to ophthalmic rimexolone 1% and ophthalmic prednisolone 1% (P=0.030 for overall group difference). Patients complained of stinging and itching associated with the application of drops more in the ophthalmic ketorolac 0.5% group than the ophthalmic rimexolone 1% group. Patient comfort was highest with ophthalmic prednisolone 1% (P=0.041 for overall group difference).[46]

Ophthalmic ketorolac 0.5% has been compared to ophthalmic diclofenac 0.1% for efficacy in relieving corneal pain following refractive surgery.[49,50] Results of a trial by Narvaez et al demonstrated that both treatment groups were effective in relieving ocular pain with no significant differences in pain relief or stinging on instillation between the treatment groups (P=0.29).[49] In another trial, ophthalmic diclofenac 0.1% was more effective than ophthalmic ketorolac 0.5% in corneal sensitivity assessment after controlling for the effects of time (P<0.01).[50] There was no difference in burning sensation between the groups (P=0.12).

None of the available ophthalmic NSAIDs have been FDA-approved for either the prevention or treatment of cystoid macular edema. A number of placebo-controlled and ophthalmic corticosteroid comparator trials evaluating the use of ophthalmic NSAIDs in cystoid macular edema have been conducted.[51-56] There are no substantive differences with ophthalmic NSAIDS compared to each other or to ophthalmic corticosteroids in the prevention or treatment of cystoid macular edema.

Several trials have demonstrated the efficacy of ophthalmic NSAIDs including flurbiprofen 0.03%, ketorolac 0.5% diclofenac 0.1%, and nepafenac 0.1% in preventing intraoperative miosis during cataract surgery.[57-60] A number of active comparator studies have demonstrated similar efficacy between the agents in preventing intraoperative miosis.

Ophthalmic ketorolac 0.5% was compared to ophthalmic diclofenac 0.1% in 60 patients for 14 days, with no significant differences reported between the treatments for the individual parameters of itching and bulbar conjunctival injection.[61] Ophthalmic ketorolac 0.5% and ophthalmic olopatadine 0.1% were compared in a randomized controlled trial (N=40). Ocular itching and hyperemia were significantly improved in both the treatment groups ($P<0.05$).[62] Itching scores were significantly lower in the ophthalmic olopatadine 0.1% group on days two, seven and 15 compared to ophthalmic ketorolac 0.5% ($P=0.018$, $P=0.007$ and $P=0.036$, respectively).

Table 3. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cataract Surgery				
Silverstein et al[22] Bromfenac 0.09% one drop in the affected eye QD vs vehicle one drop in the affected eye QD Dosing began one day before surgery (day one), continued on the day of cataract surgery (day zero) and for 14 days following cataract surgery (days one to 14).	2 DB, MC, PC, PG, RCT Patients ≥18 years of age who were only scheduled for unilateral cataract surgery with posterior chamber IOL implantation and best-corrected visual acuity of ≥20/200 in the non-study eye	N=455 15 days	Primary: Proportion of patients with cleared ocular inflammation and the absence of anterior chamber cell or flare (SOIS grade of zero) by day 15 Secondary: Proportion of patients who had no ocular pain by the subject-reported OCGA (score of zero) at day one and adverse events	Primary: The proportion of patients with cleared ocular inflammation by day 15 was significantly higher in patients treated with bromfenac compared to patients treated with placebo (46.1 vs 26.2%; P<0.0001). Significant differences in ocular inflammation between treatment groups occurred as early as day eight of treatment, but not at days one (P=0.81) or three (P=0.60). Secondary: The proportion of patients who were free of ocular pain one day following surgery was significantly higher in the bromfenac group compared to the placebo group (87.0 vs 64.7%, P<0.0001). For patients who reported ocular pain at day one, the median time to pain resolution was twice as fast in the bromfenac group compared to the placebo group (two vs four days; P value not reported). Fewer adverse events occurred in the bromfenac group in trial one (27.4 vs 42.5%) and trial two (46.9 vs 59.7%) compared to the placebo group. In trial one, the most common adverse events in the bromfenac and placebo groups, respectively, were eye inflammation (5.5 vs 13.7%), eye pain (2.7 vs 6.8%) and foreign body sensation (1.4% for both). In trial two, the most common adverse events in the bromfenac and placebo groups, respectively, were foreign body sensation (12.2 vs 13.9%), eye inflammation (10.2 vs 14.6%), vision blurred (10.2 vs 7.6%) and eye pain (8.8 vs 23.6%). Discontinuation due to an adverse event was significantly lower in the bromfenac group compared to the placebo group (5.7 vs 16%; P=0.0004).
Donnenfeld et al[23] Bromfenac 0.09% one drop in the affected eye(s) BID for 14 days vs	2 DB, MC, PC, PG, RCT Patients ≥18 years of age with uncomplicated unilateral cataract	N=527 29 days	Primary: Proportion of patients with cleared ocular inflammation (determined by anterior chamber cells and a flare grade, summed ocular	Primary: A significantly greater proportion of patients achieved complete clearance of ocular inflammation at day 15 following treatment with bromfenac compared to treatment with placebo (64.0 vs 43.3%; P<0.0001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vehicle one drop in the affected eye(s) BID for 14 days Treatment was administered starting 16 to 32 hours following surgery.	surgery (phaco-emulsification or extracapsular cataract extraction) with posterior chamber IOL implantation and summed ocular inflammation score ≥3, 16 to 32 hours following cataract extraction		inflammation score of zero in the study eye) on study day 15 Secondary: Proportion of patients with summed ocular inflammation score of zero, proportion of protocol-compliant patients with summed ocular inflammation score of zero, evaluation of primary efficacy outcome at each study visit, marked improvement (summed ocular inflammation score ≤1) in ocular inflammation at each study visit, mean cells and flare at each visit, time to resolution of ocular pain and proportion pain free, and photophobia while on bromfenac or placebo alone before administration of rescue medication adverse events and tolerability	There was a statistically significant difference in the outcome of cleared ocular inflammation for patients receiving bromfenac compared to patients receiving placebo (P<0.0001). Significantly more protocol-compliant patients treated with bromfenac experienced cleared ocular inflammation compared to patients treated with placebo (89.4 vs 80.3%; P=0.038). There was a significant greater proportion of patients with a marked improvement in ocular inflammation (summed ocular inflammation score ≤1) in the bromfenac group compared to the placebo group (85.1 vs 52.6%; P<0.0001). The median time to resolution of ocular pain following cataract surgery was two days for bromfenac compared to five days with placebo (P<0.0001). Eye irritation including burning and stinging was reported in fewer patients receiving bromfenac compared to patients receiving placebo (2.5 vs 4.7%), as was photophobia (2.0 vs 11.1%). There were no serious adverse events reported in either of the two treatment groups.
Henderson et al[24] Bromfenac 0.09% one drop in the affected eye QD	DB, MC, PC, RCT (Pooled analysis of 4 trials) Patients ≥18 years of age who were	N=1149 15 days	Primary: Proportion of patients with cleared ocular inflammation, the absence of anterior chamber cell or flare	Primary: The proportion of patients with cleared ocular inflammation by day 15 was significantly greater in the bromfenac group compared to the placebo group (51.1 vs 27.4%; P<0.0001). In addition, patients treated with bromfenac had a lower mean SOIS score at days three, eight, 15 and 22 compared to patients treated with placebo (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs bromfenac 0.18% one drop in the affected eye QD (data not reported for this dose) vs vehicle one drop in the affected eye QD Dosing began one day before surgery (day one), continued on the day of cataract surgery (day zero) and for 14 days following cataract surgery (days one to 14).	only scheduled for unilateral cataract surgery with posterior chamber IOL implantation and best-corrected visual acuity of ≥20/200 in the non-study eye		(SOIS grade of zero) by day 15 Secondary: Proportion of patients who had no ocular pain by the subject-reported OCGA (score of zero) at day one and adverse events	Secondary: On day one, the proportion of patients who were pain-free was significantly greater in the bromfenac group compared to the placebo group (84 vs 67%; P<0.0001). More patients treated with bromfenac continued to be pain-free at days three, eight and 15 compared to patients treated with placebo (91 to 96% vs 67 to 71%, respectively; P values not reported). Patients treated with bromfenac experienced significantly fewer adverse events compared to patients receiving placebo (35.1 vs 55.0%; P<0.0001). In the bromfenac and placebo groups, respectively, the most common adverse events were eye inflammation (11.8 vs 13.9%), conjunctival hyperemia (8.5 vs 3.7%), eye pain (8.2 vs 14.5%) and foreign body sensation (8.2 vs 8.0%) The proportion of patients discontinuing treatment due to adverse events was significantly higher in the placebo group compared to the bromfenac group (16.2 vs 5.2%; P<0.0001). By day 15, discontinuation rates due to lack of efficacy remained higher in the placebo group compared to the bromfenac group (32.7 vs 2.9%; P<0.0001).
Walters et al[25] Bromfenac 0.07% one drop in the affected eye(s) QD vs Placebo one drop in the affected eye(s) QD Dosing began one day before surgery, continued on the day of surgery and for 14 days after surgery.	DB, MC, PC, PRO, RCT Patients ≥18 years of age who were scheduled for unilateral cataract surgery (cataract extraction or phaco-emulsification) with posterior chamber IOL implantation without other ophthalmic surgical	N=440 15 days (plus 1 day preop)	Primary: Cleared intraocular inflammation achieved by day 15 Secondary: Proportion of patients who achieved complete clearance of ocular inflammation at day 15, the proportion of patients who were pain free at day 1, proportion of patients who achieved clearance of ocular inflammation by	Primary: Proportion of patients who achieved complete clearance of ocular inflammation by day 15, was significantly higher in the bromfenac 0.07% group (48.6% [108/222]) than in the placebo group (24.3% [53/218]; P<0.0001). Secondary: A significantly higher proportion of patients in the bromfenac 0.07% group, compared with those in the placebo group, also achieved complete clearance at day 8 (27.0% [60/222] vs. 10.1% [22/218], respectively; P<0.0001) and at day 15 (45.5% [101/222] vs. 20.6% [45/218], respectively; P<0.001). The proportion of patients who had cleared ocular inflammation was significantly greater in the bromfenac 0.07% group than in the placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	procedures		and at days 1, 3, and 8, and the proportion of patients who achieved an ocular pain score of none at day 3, at day 8, and at day 15	group by day 8 (29.7% [66/222] vs. 11.9% [26/218]; P<0.0001). A significantly greater proportion of patients were pain free in the bromfenac 0.07% group than in the placebo group at day 1 (78.8% [175/222] vs. 49.5% [108/218]; P<0.0001), and this continued through the remaining follow-up visits. The mean pain scores in the bromfenac 0.07% group were significantly lower than those in the placebo group at all followup visits (P<0.0001 for all comparisons).
Donnenfeld et al[26] Ketorolac 0.45% one drop in affected eye(s) BID on the day prior to surgery, on the day of surgery and for 14 days following surgery vs vehicle one drop in affected eye(s) BID on the day prior to surgery, on the day of surgery and for 14 days following surgery On the day of surgery, patients had a total of six drops of study medication; one drop on awakening, three drops each 20 minutes apart, starting two hours prior to surgery, one drop before discharge, and one drop 12 hours after the first dose in the morning.	2 DB, MC, PC, RCT Patients with cataracts who were scheduled to undergo unilateral phacoemulsification with implantation of a posterior chamber IOL	N=511 16 days	Primary: Proportion of patients with cleared ocular inflammation and the absence of anterior chamber cell or flare (SOIS grade of zero) by day 14 Secondary: Proportion of patients pain-free on postoperative day one, time to postoperative ocular pain resolution, proportion of patients completing the study without using any additional medications for inflammation or pain, treatment failure rate, pupil size after irrigation and aspiration	Primary: By day 14, the proportion of patients with cleared ocular inflammation was significantly greater in patients treated with ketorolac compared to patients receiving placebo (52.5 vs 26.5%; P<0.001). Secondary: On day one, significantly more patients treated with ketorolac had a no postoperative pain compared to patients receiving placebo (72.4 vs 39.7%; P<0.001). The median time to the resolution of postoperative ocular pain was one day for the ketorolac group compared to two days for the placebo group (P<0.001). The proportion of patients who completed the study without using additional medications for inflammation or pain was significantly greater with ketorolac compared to placebo (81.2 vs 57.1%; P=0.001). The rate of treatment failure was significantly greater in patients treated with placebo compared to patients treated with ketorolac on days three, seven and 14 (P≤0.001 for all). There was no statistically significant difference between the treatments with regard to pupil size after irrigation and aspiration (P=0.441).
Lane et al[27]	DB, MC, PC, RCT	N=476	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Nepafenac 0.1% one drop in the affected eye(s) TID one day prior to surgery, continuing on the day of surgery and for 14 days vs vehicle one drop in the affected eye(s) TID one day prior to surgery, continuing on the day of surgery and for 14 days Each patient also received one drop of their respective study medication 30 to 120 minutes prior to surgery and moxifloxacin TID for one to two days preoperatively and one week postoperatively.	Patients ≥18 years of age scheduled to undergo cataract extraction surgery with posterior chamber IOL implantation	16 days	Proportion of patients cured of ocular inflammation at day 14 (aqueous cells score and aqueous flare score of zero) Secondary: Comparison of cure rates by visit, proportion of patients pain-free at all visits, aqueous cells, flare and cells and flare scores	Significantly more patients treated with nepafenac were cured of ocular inflammation at day 14 compared to patients treated with placebo (62.6 vs 17.2%; P<0.0001). Secondary: Nepafenac resulted in a higher percentage of cures at all visits as compared to vehicle (P≤0.005). A greater proportion of patients in the nepafenac group were pain-free at all visits compared to placebo (P<0.0001 for all). Throughout the study, most nepafenac-treated patients were pain-free (83.1 to 93.0%) compared to less than half the vehicle-treated patients (41.6 to 46.4%). Patients treated with nepafenac experienced significantly lower mean aqueous cells scores, mean aqueous flare scores, mean aqueous cells and flare scores at all visits compared to placebo (P<0.0001 for all). No clinically relevant changes from baseline in visual acuity, ocular signs (corneal edema, bulbar conjunctival injection and chemosis), IOP or dilated fundus parameters (retina, macula, choroid, and optic nerve) were observed in either group. Slightly higher incidences of ocular hyperemia and photophobia were observed in the placebo group (P values not reported).
Maxwell et al[28] Nepafenac 0.1% one drop in the affected eye(s) QD, BID or TID beginning one day prior to surgery, continuing on the day of surgery and for 14 days vs vehicle one drop in the	DB, MC, PC, PRO, RCT Patients ≥18 years of age scheduled to undergo cataract extraction by phacoemulsification followed by posterior chamber IOL implantation	N=212 16 days	Primary: Proportion of treatment failures (≥16 aqueous cells, aqueous flare rated as severe, or ocular pain score rated as moderately severe or severe) through postoperative day 14, best-corrected visual acuity, ocular signs, IOP, surgically related	Primary: Nepafenac administered QD, BID or TID was associated with a significantly lower incidence treatment failure through day 14 compared to placebo (P≤0.0020 for all). Treatment failure rates for nepafenac QD, BID, TID were 25.0, 30.0 and 19.6%, respectively, compared to 60.3% with placebo. All nepafenac treatment groups experienced significantly lower incidences of treatment failure, compared to vehicle on days seven and 14 (P≤0.0029 and P≤0.0009, respectively). Patients receiving nepafenac TID experienced a significantly lower incidence of treatment failure by day three compared to patients receiving placebo (P≤0.0080).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
affected eye(s) QD, BID or TID beginning one day prior to surgery, continuing on the day of surgery and for 14 days Each patient also received one drop of their respective study medication 30 to 120 minutes prior to surgery and topical antibiotic therapy for one week following surgery per investigator's standard of care.			expected conditions, abnormalities during dilated fundus examinations of retina, macula, choroid and optic nerve Secondary: Cumulative proportion of treatment failures at each postoperative visit, proportion of patients with no ocular pain and inflammation by visit	Placebo-treated patients (40.7%) experienced a greater frequency of adverse events compared to patients receiving nepafenac QD, BID or TID (32.0, 24.5 and 25.9%, respectively). No serious ocular adverse events occurred during the study. Secondary: Nepafenac treatment significantly increased the proportion of patients with resolved ocular inflammation beginning on day one with TID dosing (P≤0.0208) and day three with QD dosing (P≤0.0483) compared to placebo. All nepafenac groups had significantly lower proportions of treatment failures at postoperative days three through 14 compared to the placebo group (P≤0.0220).
Koçak et al[29] Diclofenac 0.1% one drop in the affected eye(s) every six hours in three doses beginning at 6 PM on evening prior to surgery and at 90, 60, 30 and 15 minutes before surgery then QID for three to six weeks following surgery vs flurbiprofen 0.03% one drop in the affected eye(s) every six hours in three doses beginning at 6 PM on evening prior to surgery and at 90, 60, 30 and 15	AC, DB, PRO, RCT Patients undergoing extracapsular cataract extraction with IOL implantation with no preoperative complications	N=43 6 weeks	Primary: Conjunctival hyperemia scores, corneal thickness, corneal surface changes, IOP and inflammation of anterior chamber Secondary: Not reported	Primary: Both treatment groups experienced a decrease in severity of hyperemia at weeks three and six following surgery. One patient in the diclofenac group had severe conjunctival hyperemia at the final visit believed to be an allergic reaction to preservatives. The difference between the two treatment groups was not statistically significant at any time point (P>0.05 for all). At weeks one, three and six following surgery, the differences in corneal thickness were not statistically significant between treatment groups (P>0.05 for all). The mean IOP values of both groups were within normal limits throughout the study and were slightly lower in flurbiprofen group than in diclofenac group at all visits; however, the difference was not statistically significant (P>0.05). Both treatment groups showed corneal punctation at the first visit; however, the difference between groups was not statistically significant (P>0.05). One patient in the diclofenac group had marked corneal

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
minutes before surgery then QID for three to six weeks following surgery Each patient also received tobramycin 0.3% one drop in the affected eye(s) QID for one week.				punctation and this was the same patient who also had severe conjunctival hyperemia. There was no statistically significant difference between the two treatment groups at week one, three or six with regard to anterior chamber inflammation (P>0.05). Secondary: Not reported
Flach et al[30] Ketorolac 0.5% one drop in the affected eye(s) QID beginning the first postoperative day following surgery vs diclofenac 0.1% one drop in the affected eye(s) QID beginning the first postoperative day following surgery Each patient also received tropicamide 0.5% solution one drop TID for two weeks and ofloxacin 0.3% solution one drop QID for seven days following surgery.	AC, DB, PRO, RCT, SC Patients ≥21 years of age admitted for elective, unilateral, cataract surgery and IOL implantation	N=120 30 days	Primary: Subjective measurement of anterior chamber inflammation determined by anterior chamber cells and anterior chamber flare through slit-lamp biomicroscope measurements, objective measurement of anterior chamber inflammation determined by laser cell and flare meter Secondary: Toxicity during three separate postoperative visits	Primary: The two treatment groups were not statistically different at any of the three postoperative visits in terms of flare or cells as measured with the laser cell and flare meter (flare and cells as measured by laser cell and flare meter at visit three were P=0.10 and P=0.55, respectively and were P=0.95 and P=0.08, respectively, when measured by slit-lamp examinations). Secondary: There were no adverse events reported or observed during the study. There was no significant difference between the reports and descriptions of ocular discomfort upon instillation between the treatment groups (P=0.30).
Weber et al[31] Ketorolac 0.5% one drop in the affected eye(s) QID	AC, DB, MC, PG, RCT Patients ≥18 years	N=123 3 months	Primary: Aqueous flare measured with a laser flare meter on days one and seven	Primary: At day one, the mean aqueous flare was 18.50 ph/ms for the indomethacin group compared to 16.25 ph/ms for the ketorolac group. The upper limit of the 95% CI (5.50) was less than the upper limit of the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for three weeks, beginning 24 hours prior to surgery vs indomethacin 0.1%* one drop in the affected eye(s) QID for three weeks, beginning 24 hours prior to surgery	of age planning to undergo cataract surgery on one eye by phaco-emulsification with posterior chamber IOL and a preoperative flare ≤15 ph/ms measured with an laser flare meter without pharmacological pupil dilation		following cataract surgery Secondary: Aqueous flare at days 30 and 90 following surgery, change from baseline in retinal thickness measured by OCT at days 30 and 90, anterior chamber flare, conjunctival hyperemia and ciliary flush at all visits except the day of surgery, patient ratings of postsurgical pain or discomfort immediately following and 24 hours following surgery, change in the appearance of the macula and the rest of retina by dilated indirect funduscopy at days 30 and 90 and percentage of patients using concomitant medications to treat postoperative ocular inflammation	non-inferiority margin (15.00), demonstrating non-inferiority of indomethacin. When tested for superiority, the difference in the mean aqueous flare between the indomethacin and ketorolac groups at day one was not statistically significant (P=0.431). At day seven, the mean aqueous flare was 11.88 ph/ms in the indomethacin group and 15.01 ph/ms in the ketorolac group. The upper limit of the 95% CI (-0.94) was less than the upper limit of non-inferiority margin (8.00), demonstrating non-inferiority of indomethacin. When tested for superiority, indomethacin reduced aqueous flares significantly more compared to ketorolac (P=0.013). Secondary: At 30 days, the mean aqueous flare in patients treated with indomethacin was 9.2 ph/ms compared to 8.94 ph/ms in patients treated with ketorolac (P=0.559). At 90 days, the mean aqueous flare was 9.20 ph/ms in the indomethacin group and 8.12 ph/ms in the ketorolac group (P=0.571). The change from baseline in central retinal thickness at days 30 (P=0.131) and 90 (P=0.736) between the treatment groups was not statistically significant. The increase from baseline in central retinal thickness was less marked in the indomethacin group compared to the ketorolac group. No statistically significant differences were identified in the results of slit lamp examination and funduscopy between the treatment groups (data not reported). Furthermore, none of the study participants required concomitant medication to treat postsurgical inflammation. Fewer patients reported mild to moderate pain in the indomethacin group compared to the ketorolac group on the day of surgery (32.2 vs 44.3%; P=0.228) but not at day one (27.1 vs 24.6%; P=0.537); however, the differences were not statistically significant.
Duong et al[32]	AC, DB, PRO, RCT, SC	N=183	Primary: Objective findings (visual	Primary: Visual recovery scores were slightly better in the ketorolac group than in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ketorolac 0.4% one drop in the affected eye(s) QID for seven days plus gatifloxacin 0.3% one drop in the affected eye(s) QID for seven days plus prednisolone acetate 1% one drop in the affected eye(s) QID for seven days and tapered thereafter vs nepafenac 0.1% one drop in the affected eye(s) TID for seven days plus moxifloxacin 0.5% one drop in the affected eye(s) QID for seven days plus prednisolone acetate 0.125%* one drop in the affected eye(s) QID for seven days and tapered thereafter	Patients with visually significant cataract who were a candidate for cataract surgery	1 month	function, degree of inflammation in the anterior segment and complications) and subjective complaints (burning, itching, foreign body sensation and pain level after surgery) Secondary: Not reported	the nepafenac group one day postoperatively; however, this difference was not statistically significant (P value not reported). Visual acuities were comparable between the two treatment groups at one week (P=0.66) and one month (P=0.16) postoperatively. There was no difference between the two treatment groups in anterior chamber inflammation (P>0.05). Nepafenac was associated with a higher incidence of posterior capsule opacification compared to ketorolac (13 vs 5 cases; P=0.019). Ketorolac was associated with significantly greater patient satisfaction, patient compliance, and postoperative pain control compared to nepafenac (P=0.022, P=0.023 and P=0.025, respectively). Secondary: Not reported
Sandoval et al[33] Ketorolac 0.5% one drop in the affected eye(s) every five minutes, starting 15 minutes prior to surgery, then one drop in the affected eye(s) QID for one week, then BID for three weeks vs	DB, PRO, RCT, SC Patients ≥40 years of age scheduled to undergo routine phacoemulsification and IOL implantation	N=40 4 weeks	Primary: Best-corrected visual acuity, slit-lamp examination, IOP, laser cell and flare measurements and subjective patient tolerance evaluated postoperatively at days one, seven and 30 Secondary:	Primary: There were no significant differences between the two treatment groups at any time point (day one, seven or 30 postoperatively) with regard to mean, median and range of best-corrected visual acuity, IOP, slit-lamp cell count, laser flare-cell meter cells and flare over time (P values not reported). There was a significant improvement in best-corrected visual acuity in both the treatment groups compared to baseline at one week and 30 days (P<0.001). There were no significant differences in IOP in either of the treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ketorolac 0.4% one drop in the affected eye(s) every five minutes, starting 15 minutes prior to surgery, then one drop in the affected eye(s) QID for one week, then BID for three weeks Each patient received ofloxacin 0.3% one drop in the affected eye(s) QID for one week starting right after surgery.			Adverse events	groups (P values not reported). A significantly greater proportion of patients in the ketorolac 0.5% group reported ophthalmic symptoms (deep eye pain, light sensitivity, itching, foreign body sensation, stinging and burning) compared to patients in the ketorolac 0.4% group (70 vs 40%; P=0.03) at day one postoperatively. There were no significant differences in the reporting of ophthalmic symptoms between the two treatment groups at one week or 30 days (P values not reported). Secondary: No adverse events were reported in either of the two treatment groups (P values not reported).
Modi et al[34] Nepafenac 0.3% one drop in the affected eye(s) QD vs nepafenac 0.1% one drop in the affected eye(s) TID vs vehicle one drop in the affected eye(s) QD vs vehicle one drop in the affected eye(s) TID Dosing started the day	AC, DB, MC, PC, PG, RCT Patients ≥18 years of age who had a planned cataract extraction by phacoemulsification with the implantation of a posterior chamber IOL	N=2,022 16 days	Primary: Percentage of patients at day 14 whose inflammation had resolved Secondary: Percentage of patients who were pain free at day 14, the percentage of cumulative cures by visit, the cumulative pain-free rates by visit, the percentage of patients who were declared treatment failures at each visit, and the percentage of patients in each treatment group who achieved clinical success	Primary: The distribution of demographic and baseline characteristics were well balanced, with no clinically relevant differences between groups. Based on a prespecified margin of -10%, nepafenac 0.3% QD was noninferior to nepafenac 0.1% TID for the prevention and treatment of ocular inflammation 14 days after cataract extraction (95% CI, -5.73 to 3.17; no P value given). Significantly more patients in the nepafenac 0.3% and nepafenac 0.1% groups than patients in the respective vehicle groups achieved a cure at day 14 (both P<0.0001). Secondary: From day seven, the observed cumulative percentage of patients who were cured in the nepafenac 0.3% group was higher than in the nepafenac 0.3% vehicle group (P<0.0001 for pairwise comparisons at day 7 and day 14). The percentage of patients cured was also higher in the nepafenac 0.1% group than in the nepafenac 0.1% vehicle group beginning at postoperative day three (P<0.0001 for pairwise comparisons at days 3, 7, and 14).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
before surgery, continued on the day of surgery and for 14 days thereafter. On the day of surgery, one additional drop was instilled 30 to 120 minutes before surgery.				Nepafenac 0.3% QD was noninferior to nepafenac 0.1% TID for the prevention and treatment of ocular pain 14 days after cataract extraction. Significantly more patients in the nepafenac 0.3% and nepafenac 0.1% groups were pain free at day 14 than patients in the respective vehicle groups (both P<0.0001). The cumulative percentage of patients who were pain free in the nepafenac 0.3% and nepafenac 0.1% groups was higher than in their respective vehicle groups at all postoperative visits from day 1 through day 14 (P<0.0001 for all pairwise comparisons at each study visit). The cumulative clinical success rate at day 14 was 85.6% in the nepafenac 0.3% QD (N=691) and nepafenac 0.1% TID (N=694) groups; the rates were 43.1% (N=85) and 47.8% (N=98) in the respective vehicle groups. The cumulative percentage of patients who were clinical successes was greater in the nepafenac 0.3% group than in the nepafenac 0.3% vehicle group at all postoperative visits (P=0.0264 at day 1; P<0.0001 at days 3, 7, and 14). The percentage of clinical successes was greater in the nepafenac 0.1% group than in the nepafenac 0.1% vehicle group on days 1, 3, 7, and 14 (P<0.0001 at all time points except day one). The cumulative percentage of patients assessed as treatment failures in the nepafenac 0.3% and nepafenac 0.1% groups was lower than in the respective vehicle groups at all postoperative visits (P≤0.0012 in each pairwise comparison for every study visit).
Maca et al[35] Diclofenac 0.1% (preservative-free) one drop in the affected eye(s) QID, starting on the first postoperative day following surgery vs	AC, OL, PG, PRO, RCT, SB Patients ≥40 years of age scheduled for phaco-emulsification surgery of cataract with posterior chamber IOL	N=102 4 weeks	Primary: Anti-inflammatory effect (via anterior chamber flare), retinal thickness (mean foveal thickness), tolerability(with use of a visual analog scale), subjective ocular discomfort, conjunctival hyperemia, visual acuity	Primary: There was no significant difference between treatment groups with regard to the change in anterior chamber flare. All groups experienced a significant increase from baseline following surgery (P<0.001 for all) and thereafter a decrease at each postoperative time point (P<0.001 for all). There was no significant change in retinal thickness on day one (150.8±22.4 µm), after one week (155.9±20.4 µm), or one month (152.7±20.0 µm). No patients had visible cystoid macular edema on scans within one month following surgery. There was no correlation

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
diclofenac 0.1% one drop in the affected eye(s) QID, starting on the first postoperative day following surgery vs ketorolac 0.5% one drop in the affected eye(s) QID, starting on the first postoperative day following surgery	implantation, no history of intraocular inflammation or uveitis, pseudoexfoliation syndrome, significant posterior segment disease involving the macular region, and previous ocular surgery or recent topical glaucoma treatment		and intraocular pressure Secondary: Not reported	between mean foveal thickness and anterior chamber flare among treatment groups. Conjunctival hyperemia was significantly increased on day one in all three treatment groups compared to baseline values (P<0.01 for all groups), with no differences between treatment groups. The incidence of conjunctival injection in all groups decreased from day one to one week (P=0.03 for all groups). Patients receiving preservative-free diclofenac experienced less conjunctival injection compared to the groups receiving preserved diclofenac or ketorolac (P=0.029). In patients receiving preservative-free diclofenac, the VAS scores for tolerability remained stable, whereas patients receiving preserved diclofenac and preserved ketorolac experienced a rise in scores (less comfortable) from one day to one week and one week to one month (P=0.005 and P<0.001, respectively). These scores were also higher than those in the preservative-free diclofenac group (one week, P=0.001, and one month, P=0.033). Patients treated with preservative-free diclofenac experienced less local discomfort compared to patients treated with preserved diclofenac and preserved ketorolac (P=0.02 and P=0.012, respectively). One week following surgery, only patients receiving preservative-free diclofenac reported less local discomfort compared to day one (P=0.008). At one month, there was no difference in ocular discomfort scores between treatment groups (P values not reported). There was no difference between treatment groups with regard to visual acuity at any time point following surgery. All three treatments significantly reduced IOP at one month after surgery (P=0.001), with no significant differences between treatments. Secondary: Not reported
Bucci et al[36]	AC, DB, OS, SC	N=121	Primary: PGE_2 concentrations	Primary: Treatment with ketorolac was associated with the greatest inhibition of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bromfenac 0.09% one drop in the affected eye(s) BID one day preoperatively and four doses administered 15 minutes apart one hour prior to phacoemulsification vs ketorolac 0.45% one drop in the affected eye(s) BID one day preoperatively and four doses administered 15 minutes apart one hour prior to phacoemulsification vs nepafenac 0.1% one drop in the affected eye(s) BID one day preoperatively and four doses administered 15 minutes apart one hour prior to phacoemulsification	Patients previously diagnosed with a cataract sufficient enough to warrant extraction and who were scheduled to undergo phacoemulsification and IOL implantation	1 day	Secondary: Not reported	PGE_2 compared to treatment with bromfenac and nepafenac. The mean (±SD) concentrations of PGE_2 in the vitreous humor samples were 224.80±164.87 pg/mL with ketorolac compared to 288.70±226.05 pg/mL with bromfenac (P=0.14) and 320.4±205.6 pg/mL with nepafenac (P=0.025). The difference between bromfenac and nepafenac was not significantly different (P=0.516). Secondary: Not reported
Roberts et al[37] Diclofenac 0.1% one drop in the affected eye(s) QID for one week then one drop in the affected eye(s) BID for three weeks	AC, DB, RCT Patients who underwent phacoemulsification with posterior chamber IOL implantation	N=52 1 month	Primary: Subjective postoperative inflammation evaluation by slit-lamp assessment of cell and flare and objective evaluation by measurement of cell and flare with a laser of cell	Primary: Diclofenac treatment was associated with lower inflammation scores compared to prednisolone acetate treatment at one week and one month following surgery; however, the results were not statistically significant (flare; P=0.138 and P=0.196, cell; P=0.588 and P=0.218, slit-lamp score; P=0.139 and P=0.521, respectively). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs prednisolone acetate 1% one drop in the affected eye(s) QID for one week then one drop in the affected eye(s) BID for three weeks Each patient also received gentamicin sulfate eye drops.			and flare meter on one day, one week and one month following surgery Secondary: IOP	Both treatment groups experienced a reduction from baseline in IOP at one week and one month. The mean decrease was significantly greater with diclofenac compared to prednisolone acetate (4.7 vs 0.9 mm Hg; P=0.007). The difference between the two groups, after adjusting for the baseline difference in the analysis, was not statistically significant (P=0.074).
Reddy et al[38] Diclofenac 0.1% one drop in the affected eye(s) six times a day vs dexamethasone 0.1% one drop in the affected eye(s) six times a day Each patient also received tropicamide 1% for preoperative dilation and it was also included in the postoperative regimen.	AC, DB, PRO, RCT Patients >25 years of age who underwent uncomplicated extracapsular cataract extraction with posterior chamber IOL implantation	N=60 21 days	Primary: Aqueous flare and cells in anterior chamber, conjunctival congestion and corneal edema on days one, three, seven, 14 and 21 following surgery and severity of inflammation graded on a four-point scale Secondary: Not reported	Primary: There was no significant difference in anti-inflammatory activity between the two treatment groups on days three, seven, 14 or 21 following surgery for signs of flare, cells in the anterior chamber, conjunctival congestion and corneal edema (P values not reported). The time to achieve anti-inflammatory activity was significant (P<0.0001). The rate of improvement did not differ significantly between the two treatment groups (P values not reported). In terms of response of cells in the anterior chamber, the trend for improvement appeared to be faster and greater in magnitude with dexamethasone compared to diclofenac (P values not reported). Best corrected visual acuity did not differ statistically between treatment groups (P values not reported). Secondary: Not reported
Laurell et al[39] Diclofenac 0.1% one drop in the affected eye(s) QID for one week following	AC, DB, PRO, RCT, SC Patients 64 to 85 years of age	N=180 4 years	Primary: Inflammatory reaction in the anterior chamber measured with laser flare photometry	Primary: There were no statistically significant differences in inflammation between the three treatment groups on first postoperative day (P=0.830).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
surgery, then one drop in the affected eye(s) BID for three weeks vs dexamethasone 0.1% one drop in the affected eye(s) QID for one week following surgery, then one drop in the affected eye(s) BID for three weeks vs vehicle one drop in the affected eye(s) QID for one week following surgery, then one drop in the affected eye(s) BID for three weeks	scheduled to undergo cataract surgery by phacoemulsification and IOL implantation		preoperatively and at one, three and eight days, two and four weeks, two and six months, and one, two and four years postoperatively and inflammatory symptoms Secondary: Visual acuity, rate of striate keratopathy, IOP and capsulotomy rate	The flare values at three and eight days, two weeks and one month following surgery were significantly lower in the diclofenac and dexamethasone groups compared to the placebo group (P≤0.05 for all). There were no significant differences between diclofenac and dexamethasone at any observation time (P values not reported). Inflammatory symptoms were reported in 11 of 60 patients (18.3%) on day three and in 18 of 59 patients (30.5%) at day eight in the placebo group. The rate of patients with inflammatory symptoms was greater in the placebo group at day three (P<0.001) and day eight (P<0.001) but not at two weeks and thereafter. There were no significant differences between diclofenac and dexamethasone treatment groups at any observation time. Secondary: With regard to visual acuity, the only significant difference between the treatment groups was at day eight when visual acuity was better in the dexamethasone group compared to the placebo group (81.7 vs 62.7%; P<0.05). At day eight, striate keratopathy was more frequent in the placebo group compared to the other two treatment groups (P=0.01). There were no subsequent corneal reactions. There were no epithelial complications found in any of the three treatment groups. The median IOP was significantly higher in the dexamethasone group than in the placebo group after eight days (16 vs 13 mm Hg; P<0.05). At one month IOP was slightly higher in dexamethasone group compared to the diclofenac group (15 vs 14 mm Hg; P<0.05). No significant IOP differences were reported at other observation times. The rate of Nd:YAG laser posterior capsulotomies were equal in the three treatment groups after two years. It was significantly lower in the placebo group than in the diclofenac group after four years (P<0.05).
Holzer et al[40]	DB, PRO, RCT	N=60	Primary: Signs and symptoms of	Primary: There was no statistically significant difference between the two groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ketorolac 0.5% one drop in the affected eye(s) QID starting 24 hours following surgery for one week, then one drop in the affected eye(s) BID for three weeks vs loteprednol 0.5% one drop in the affected eye(s) QID starting 24 hours following surgery for one week, then one drop in the affected eye(s) BID for three weeks Each patient also received ofloxacin 0.3% one drop in the affected eye(s) QID starting three days before surgery, one drop perioperatively, at completion of surgery and one drop in the affected eye(s) QID immediately following surgery.	Patients >18 years of age scheduled to have cataract extraction with posterior chamber IOL implantation	30 days	inflammation documented by external slit-lamp examination, IOP, Kowa cell and flare measurements on days one, four, seven and 30 Secondary: Not reported	in any of the ocular symptoms including deep eye pain, photophobia, itching, foreign-body sensation, stinging and burning (P values not reported). There were no statistically significant differences between the ketorolac and loteprednol groups in terms of preoperative laser cell and flare meter evaluation of cells and flare (P=0.83 and P=0.92, respectively). The mean cell and flare values evaluated by laser cell and flare meter at day one was higher in the ketorolac group compared to the loteprednol group (P=0.72 and P=0.67, respectively). The mean cell measurement by laser cell and flare meter at week one, was 3.96 in the ketorolac group and 4.89 in the loteprednol group (P=0.16). The mean flare measurement at week one was 1.43 in the ketorolac group and 0.94 in the loteprednol group (P=0.61). The mean IOP in both groups ranged from 12 to 16 mm Hg. Two patients in the loteprednol group had IOPs of 23 and 24 mm Hg one month postoperatively. These two patients had elevated preoperative IOPs of 25 and 24 mm Hg, respectively (P values not reported). Secondary: Not reported
Solomon et al[41] Ketorolac 0.5% one drop in the affected eye(s) QID starting 24 hours following surgery for one week and then BID for remainder of study vs	AC, DB, PRO, RCT Patients >18 years of age scheduled to undergo cataract extraction with posterior chamber IOL implantation	N=36 30 days	Primary: Signs and symptoms of inflammation, IOP, visual acuity, slit-lamp cell and flare, and Kowa cell and flare measurements evaluated at one, four, seven and 30 days postoperatively	Primary: Subjective measurement of inflammation by slit-lamp measurements of cell and flare were not significantly different between the two groups (P=0.17 and P=0.48, respectively). Objective measurement of cell and flare using Kowa cell and flare meter did not significantly differ between the two groups (P=0.17 and P=0.48, respectively). The cell measurements at visit two (postoperative day one) in the ketorolac and rimexolone groups were 17.5 and 8.3, respectively (P=0.28). The flare measurements at visit two in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
rimexolone 1% one drop in the affected eye(s) QID starting 24 hours following surgery for one week and then BID for remainder of study Each patient also received ofloxacin QID (duration not reported).			Secondary: Not reported	ketorolac and rimexolone groups were 18.3 and 4.7, respectively (P=0.17). There were no differences in IOP reported between treatment groups (P values not reported). Visual acuity measurements at each visit and the overall improvement in visual acuity were similar in both groups (P values not reported). No significant difference was reported between the two groups in terms of ocular symptoms (P values not reported). Secondary: Not reported
Simone et al[42] Ketorolac 0.5% one to two drops in the affected eye(s) QID on week one, TID on week two, BID on week three and QD on week four vs prednisolone acetate 1% one to two drops in the affected eye(s) QID on week one, TID on week two, BID on week three and QD on week four Each patient also received ofloxacin one drop in the affected eye(s) QID for one week.	DB, RCT, SC Patients who underwent extracapsular cataract extraction and posterior chamber IOL implantation	N=59 4 weeks	Primary: Intraocular anti-inflammatory efficacy (assessed by lid edema, lid injection, conjunctival injection, corneal edema, ciliary flush, and anterior chamber cells) and analgesic efficacy (assessed by patient reported pain severity, pain frequency, total symptom sum and overall global improvement) Secondary: Not reported	Primary: There were no statistically significant differences between the two groups in any measure of anti-inflammatory efficacy, with the exception of anterior chamber cells. The prednisolone acetate group had fewer cells in the anterior chamber compared to the ketorolac group at seven days (P=0.0073). At 28 days, there was no significant difference between the treatments (P=0.23). The ketorolac group had less frequent and severe pain symptoms at day 28 compared to the prednisolone group; however, the difference was not statistically significant (P value not reported). There were no statistically significant differences between the two treatment groups in terms of sum of symptoms, overall global improvement and IOP (P values not reported). There were no serious adverse events during the course of the study in either of the two treatment groups and no adverse event was considered to be treatment related (P values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
El-Harazi et al (abstract)[43] Diclofenac 0.1% one drop in the affected eye(s) QID for one week, then BID for next three weeks vs ketorolac 0.5% one drop in the affected eye(s) QID for one week, then BID for next three weeks vs prednisolone acetate 1% one drop in the affected eye(s) QID for one week, then BID for next three weeks	AC, DB, RCT Patients undergoing phacoemulsification with posterior chamber IOL implantation	N=58 28 days	Primary: Flare, cells and IOP on postoperative days one, seven and 28 Secondary: Medication-related complications	Primary: There were no statistically significant differences in flare or cell counts or change in flare or cell counts from baseline between the treatment groups (P values not reported). There were no statistically significant differences in IOP or in change in IOP from baseline between the three treatment groups (P values not reported). Secondary: There were no medication-related complications observed at any time during the course of study (P values not reported).
Ostrov et al[44] Ketorolac 0.5% one drop in the affected eye(s) TID starting one day before surgery and for four weeks following surgery vs dexamethasone 0.1% one drop in the affected eye(s) TID starting one day before surgery and for four weeks following surgery	AC, MC, RCT, SB Patients who underwent routine extracapsular cataract extraction or phaco-emulsification and posterior chamber IOL implantation	N=157 6 weeks	Primary: Signs of anterior-segment inflammation-primarily cells and flare in the anterior chamber observed by slit-lamp biomicroscopy, fluorescein leakage across blood-aqueous barrier measured by fluorophotometry, rating of efficacy by investigator, IOP, visual acuity and adverse events	Primary: There were no statistically significant differences between the three groups in terms of infiltration of cells into the anterior chamber on days one to two, day five, week two, week four or week six (P=0.59, P=0.51, P=0.08, P=0.32 and P=0.37, respectively). There were no statistically significant differences between the three groups in terms of anterior chamber flare on days one to two, day five, week two, week four or week six (P=0.40, P=0.09, P=0.45, P=0.09 and P=0.70, respectively). The postoperative elevation in fluorescein concentration was significantly lower in the ketorolac group than the two corticosteroid groups at day five and week two (P≤0.001 and P=0.016, respectively). There were no differences between the prednisolone acetate and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs prednisolone acetate 1% one drop in the affected eye(s) TID starting one day before surgery and for four weeks following surgery Seventy-nine percent of patients also received perioperative subconjunctival injections of a glucocorticoid (e.g., betamethasone or equivalent) and 82% of patients received an antibiotic.			Secondary: Other clinical signs of inflammation (lid edema and hyperemia)	dexamethasone groups at day five (P=0.53) or week two (P=0.77). Ketorolac, prednisolone acetate and dexamethasone groups had mean scores ranging from 86 to 91 for overall effectiveness (P=0.32) and 87 to 91 for overall acceptability (P=0.46). There were no significant differences between the three groups at any visit with respect to IOPs and visual acuity tests (P≥0.33 for both). Two of the six adverse events were treatment-related. One patient in the dexamethasone group had a moderate allergic reaction at weeks two and four and one patient in the ketorolac group developed severe uveitis (P values not reported). Secondary: The ketorolac group had higher conjunctival hyperemia scores compared to the prednisolone acetate group at week two (P=0.04 among groups).
Trinavarat et al (abstract)[45] Ketorolac one drop in the affected eye(s) QID vs fluorometholone one drop in the affected eye(s) QID vs prednisolone acetate one drop in the affected eye(s) QID	AC, PRO, RCT, SB Patients undergoing phacoemulsification	N=120 28 days	Primary: Visual acuity, IOP, slit-lamp biomicroscopy, grading of cells and flare in anterior chamber and ocular symptoms Secondary: Not reported	Primary: The number of eyes with a minimal amount of cells in the anterior chamber was significantly lower with prednisolone acetate compared to ketorolac on days seven (11 vs 20; P=0.008) and 14 (23 vs 31; P=0.015). Similarly, more patients treated with fluorometholone had a minimal amount of cells in the anterior chamber on day seven compared to patients receiving ketorolac (11 vs 21; P=0.011). The IOP was significantly higher in the prednisolone acetate group compared to the ketorolac group on day 21 (14.6 vs 12.2 mm Hg; P=0.016). One eye in the prednisolone group had an IOP of 32 mm Hg. Burning sensation was reported frequently in the ketorolac group (P values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hirneiss et al[46] Ketorolac 0.5% in the affected eye(s) per taper schedule as follows: six drops on days one to three, five drops on days four to 10, four drops on days 11 to 14, three drops on days 15 to 18, two drops on days 19 to 21 and then one drop on days 22 to 28 vs prednisolone acetate 1% in the affected eye(s) per taper schedule as follows: six drops on days one to three, five drops on days four to 10, four drops on days 11 to 14, three drops on days 15 to 18, two drops on days 19 to 21 and then one drop on days 22 to 28 vs rimexolone 1% in the affected eye(s) per taper schedule as follows: six drops on days one to three, then five drops on days four to 10, then four	DB, PRO, RCT, SC Patients ≥18 years of age who underwent elective, unilateral extracapsular cataract extraction using phacoemulsification and implantation of a posterior chamber IOL	N=45 28 days	Primary: Conjunctival hyperemia, corneal edema, best-corrected visual acuity, measurement of IOP, standardized slit-lamp examination of the anterior segment of the eye and cells and flare, stereoscopic dilated retinal examination with the biomicroscope and report of patient comfort or discomfort on postoperative days one, three, five, 14 and 28 Secondary: Not reported	Primary: Overall aqueous flare in the anterior chamber was significantly lower in the ketorolac group followed by the prednisolone acetate and rimexolone groups (P=0.008). Regarding conjunctival hyperemia, most hyperemia was observed in the ketorolac group, followed by rimexolone and prednisolone acetate groups. Prednisolone acetate treatment was associated with the lowest occurrence conjunctival hyperemia followed by rimexolone and ketorolac treatments (P=0.002 for overall group difference). Aqueous cells and corneal edema did not differ among the three groups (P=0.165 and P=0.311, respectively). There were no significant differences in pre- and postoperative visual acuity measurements between the groups (P=0.183). The ketorolac group had a significantly higher mean IOP followed by the rimexolone group. Prednisolone acetate had the lowest IOP values of the three groups (P=0.030 for overall group difference). More patients complained of stinging and itching in the ketorolac group compared to the rimexolone group. Patient comfort was highest with the prednisolone acetate group (P=0.041 for overall group difference). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
drops on days 11 to 14, then three drops on days 15 to 18, then two drops on days 19 to 21 and then one drop on days 22 to 28 Patients received antibiotic eye drops containing polymyxin-B, neomycin and gramicidin one drop in the affected eye(s) QID for first three days following surgery.				
Guzey et al (abstract)[47] Ketorolac/tobramycin vs fluorometholone/ tobramycin	AC, PRO, RCT, SC Patients undergoing phacoemulsification cataract extract with sclera tunnel incision	N=60 2 weeks	Primary: Burning/stinging sensation, blurred vision, ocular discomfort, conjunctival hyperemia, anterior chamber flare, and anterior chamber cells assessed preoperatively and postoperatively on days one (baseline), two, three, seven and 14 Secondary: Not reported	Primary: There was no statistically significant difference between the two treatment groups in terms of ocular inflammation at any of the postoperative visits (P values not reported). Both treatment regimens were well tolerated by patients (P values not reported). Secondary: Not reported
Ramakrishnan et al (abstract)[48] Nepafenac 0.1% vs ketorolac 0.4%	AC, PRO, RCT Patients with low risk factors for CME undergoing phacoemulsification	N=200 30 days	Primary: Change in CMT at the 30th postoperative day and the incidence of possible subclinical CMT (increase of >10 and >40 µm from baseline) on OCT	Primary: Change in CMT at 30 days postoperative was comparable for both the nepafenac 0.1% group and the ketorolac 0.4% group (P=0.43). The incidence of possible subclinical CMT was also comparable for both groups (P=0.18). The incidence of possible subclinical CME was 22.7%. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Incidence of definite subclinical CME on OCT (>40 µm increase in CMT from baseline) and clinically significant CME	No patients developed clinical CME or definite subclinical CME.
Corneal Refractive Surgery				
Narvaez et al (abstract)[49] Diclofenac 0.1% one drop in one eye every four hours while awake for 24 hours following surgery vs ketorolac 0.5% one drop in the other eye every four hours while awake for 24 hours following surgery	AC, DB, PRO, RCT, SC Patients undergoing elective, bilateral simultaneous radial keratotomy	N=30 1 day	Primary: Postoperative ocular pain and discomfort recorded before and 15 minutes following instillation (using VAS scale) Secondary: Not reported	Primary: Ketorolac and diclofenac were both effective in relieving postoperative pain (P value not reported). There was no significant difference in pain relief, or stinging on instillation between the two treatment groups (P=0.29). Secondary: Not reported
Seitz et al[50] Diclofenac 0.1% one drop in one eye every five minutes for a total of seven drops and one drop of placebo in the other eye every five minutes for a total of seven drops vs ketorolac 0.5% one drop in one eye every five minutes for a total of seven drops	AC, DB, PC, PG Patients 22 to 60 years of age	N=15 2 days	Primary: Assessment of corneal sensitivity prior to instillation, immediately following instillation and after termination of drop application and subjective evaluation of burning sensation following each drop application Secondary: Not reported	Primary: Ketorolac and diclofenac both significantly decreased corneal sensitivity compared to placebo (P<0.01 for both). Diclofenac was significantly more effective compared to ketorolac after controlling for the effects of time (P<0.01). Diclofenac decreased corneal sensitivity to a lower level (47.3±0.7 mm) compared to ketorolac (51.0±0.7 mm) after 30 minutes (P value not reported). The mean duration of decreased corneal sensitivity was significantly longer in the diclofenac group compared to the ketorolac group (P<0.01). There was no significant difference between the two groups with regard

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
and one drop of placebo in the other eye every five minutes for a total of seven drops				to subjective grading of perceived burning sensation (P=0.12). There was no reduction in burning sensation over time with either ketorolac or diclofenac compared to placebo (P=0.12 and P=0.99, respectively). Secondary: Not reported
Cystoid Macular Edema				
Rho et al (abstract)[51] Diclofenac 0.1% one drop in the affected eye(s) QID vs ketorolac 0.5% one drop in the affected eye(s) QID	AC, PRO, RCT Patients with clinical cystoid macular edema after phaco-emulsification cataract extraction with posterior chamber IOL	N=34 26 weeks	Primary: Improvement in cystoid macular edema and visual acuity Secondary: Not reported	Primary: There was a significant reduction in cystoid macular edema and a significant improvement in visual acuity in both groups. By 26 weeks, 16 patients in the diclofenac group had a reduction in cystoid macular edema compared to 14 patients in the ketorolac group (89 vs 88%; P=0.92). At 26 weeks, 14 patients in the diclofenac group and 12 patients in the ketorolac group experienced a resolution of cystoid macular edema (78 vs 75%; P=0.86). The mean time to initial cystoid macular edema reduction was 7.5 weeks with diclofenac and eight weeks with ketorolac (P=0.41). The mean time to cystoid macular edema resolution was 13.6 weeks with diclofenac and 12.8 weeks with ketorolac (P=0.49). Secondary: Not reported
Singal et al (abstract)[52] Ketorolac 0.5% plus vehicle vs	DB, PRO, RCT Patients with clinical cystoid macular edema occurring at least six weeks following	N=10 90 days	Primary: Improvement in Early Treatment Diabetic Retinopathy Study Snellen equivalent vision and resolution of cysts on clinical examination	Primary: There were no statistically significant differences between the two treatment groups in the outcomes measures at any visit (P values not reported). There were no significant differences between the two treatment groups in the subgroup analysis of patients with chronic cystoid macular edema

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ketorolac 0.5% plus prednisolone acetate 1% Dosing regimens were not reported.	cataract extraction		Secondary: Not reported	(P values not reported). Secondary: Not reported
Miyake et al[53] Diclofenac 0.1% one drop in the affected eye(s) three hours, two hours, one hour and 30 minutes prior to surgery and TID for eight weeks following surgery vs fluorometholone 0.1% one drop in the affected eye(s) three hours, two hours, one hour and 30 minutes prior to surgery and TID for eight weeks following surgery Each patient was also receiving oral and topical antimicrobial medications.	AC, MC, OL, PRO Patients between 60 and 70 years of age with an indication for unilateral cataract surgery	N=106 8 weeks	Primary: Visual acuity, IOP, amount of anterior chamber flare and cells measured by laser flare-cell photometry and severity of cystoid macular edema determined by fluorescein fundus angiography Secondary: Not reported	Primary: There was no significant difference between the two groups in the change in visual acuity at any time point. Both groups experienced significantly lower IOPs at three days, and one, two, five and eight weeks following surgery compared to preoperative values (P<0.05 for all time points). Treatment with diclofenac was associated with a significantly lower flare in the anterior chamber at three days, and one, two, five and eight weeks following surgery compared to treatment with fluorometholone (P<0.01 for all). Both treatment groups experienced a statistically significant increase in flare in eyes with cystoid macular edema at three days, and one, two, five and eight weeks following surgery compared to eyes without cystoid macular edema (P<0.001). There was a statistically significant increase in flare in eyes with and without cystoid macular edema in the fluorometholone group compared to the diclofenac group (P<0.05 to P<0.01). More patients in the fluorometholone group developed cystoid macular edema compared to the diclofenac group over eight weeks of treatment (54.7 vs 5.7%; P<0.001). Secondary: Not reported
Heier et al[54] Ketorolac 0.5% one drop	AC, DB, PRO, RCT Patients diagnosed	N=28 4 months	Primary: Snellen visual acuity, contrast sensitivity,	Primary: There was a significant improvement in Snellen visual acuity with combination therapy compared to prednisolone acetate at all visits

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
in the affected eye(s) QID vs prednisolone acetate 1% one drop in the affected eye(s) QID vs ketorolac 0.5% plus prednisolone acetate 1% one drop in the affected eye(s) QID Study medications were tapered at the rate of one drop per week when cystoid macular edema was resolved or for three months, whichever occurred first.	with acute clinical cystoid macular edema occurring after phaco-emulsification and posterior chamber IOL implantation		Amsler grid, slit-lamp examination, dilated fundus examination and fluorescein angiography Secondary: Not reported	(P<0.05 for all time points). In addition, combination therapy significantly improved visual acuity compared to ketorolac alone at visits four (P=0.006) and five (P=0.042). There was no significant difference in the number of patients receiving ketorolac or prednisolone acetate who experienced a two-line or greater change from baseline in visual acuity during the study (P values not reported). There was a significant difference for the combination therapy group compared to the prednisolone acetate group at visits two, three, four and five (P≤0.05 for all) and compared to the ketorolac group at visits four and five (P=0.017 and P=0.012 respectively). Fifty percent of patients in the prednisolone acetate group, 67% of patients in the ketorolac group and 89% of patients in the combination therapy group achieved a two-line or greater improvement in Snellen acuity. Sixty five percent of patients experienced an improvement in contrast sensitivity at final visit compared to baseline (50, 55 and 89% in the prednisolone acetate, ketorolac, and combination therapy groups, respectively; P values not reported). Most patients experienced an improvement in fluorescein angiography compared to baseline (50, 55 and 77% in the prednisolone acetate, ketorolac and combination groups, respectively; P values not reported). Recurrence of cystoid macular edema was noted in one patient from the ketorolac group and one patient from the combination therapy group, after an initial two-line improvement in visual acuity. Secondary: Not reported
Wittpenn et al[55] Ketorolac 0.4% plus prednisolone acetate 1%	AC, MC, PRO, RCT, SB Patients scheduled	N=546 6 weeks	Primary: Cystoid macular edema incidence measured by slit-lamp biomicroscopy	Primary: Five patients in the prednisolone acetate group had clinically apparent cystoid macular edema compared to zero patients in the combination group based on slit-lamp biomicroscopy (P=0.032).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
one drop in the affected eye(s) QID for four weeks postoperatively (patients in this group also received ketorolac 0.4% one drop in the affected eye(s) QID for three days preoperatively) vs prednisolone acetate 1% one drop in the affected eye(s) QID for four weeks Each patient also received ketorolac 0.4% one drop in the affected eye(s) every 15 minutes for a total of four doses, one hour before surgery.	to undergo phaco-emulsification with no recognized cystoid macular edema risks (diabetic retinopathy, retinal vascular disease, or macular abnormality)		and OCT Secondary: Retinal thickness as measured by OCT, Snellen best-corrected visual acuity, contrast sensitivity and adverse events	Based on OCT analysis, no patients in the combination group and six patients in the prednisolone acetate group developed definite or probable cystoid macular edema (P=0.018). Significantly fewer patients in the combination treatment group were identified with possible cystoid macular edema based on OCT compared to the prednisolone acetate group (2.2 vs 6.0%; P=0.037). Secondary: Mean retinal thickening in the combined treatment group was lower than in the prednisolone acetate group (3.9 vs 9.6 µm; P=0.003). Significantly more patients in the prednisolone acetate group than in the combination group had a >10 µm of retinal thickening on OCT (49.0 vs 26.4%; P<0.001). The prednisolone acetate group had a significantly higher incidence of retinal thickening of ≥15 µm compared to the group receiving combination treatment (P<0.001). The incidence of thickening of ≥25 µm and ≥40 µm was higher in the prednisolone acetate group than in the combination treatment group; however, the difference was not statistically significant (P=0.056 and P=0.069, respectively). In the combination group, 1.3% of patients had best-corrected visual acuity worse than 20/40 at week four compared to 2.5% of patients in the prednisolone acetate group (P=0.360). The difference in contrast sensitivity between the two treatment groups was not statistically significant (P≥0.581). Burning/stinging/tearing was the most commonly reported adverse event in the combination group, whereas, transient elevations in IOP were the most commonly reported adverse event in the prednisolone acetate

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				group. There were two serious adverse events, both in the prednisolone acetate group. One patient developed endophthalmitis and one patient died due to a cause unrelated to study medication.
Sivaprasad et al[56] Diclofenac 0.1% vs fenoprofen 1% vs flurbiprofen 0.03% vs indomethacin 25 mg (oral) vs ketorolac 0.5% vs prednisolone acetate 1% vs vehicle	SR Seven trials; three studied acute cystoid macular edema and four trials compared NSAIDs to placebo in chronic cystoid macular edema	N=266 4 to 12 weeks	Primary: Two-line or greater improvement in Snellen visual acuity, persistence of improvement of vision one month following discontinuation of treatment Secondary: Proportion of patients with improvement in leakage on fundus fluorescein angiography, proportion of participants with improved contrast sensitivity and quality of life	Primary: The mean time for a two-line improvement in Snellen visual acuity and resolution of cystoid macular edema was similar between the diclofenac and ketorolac groups. There was minimal evidence of any difference between ketorolac and placebo in achieving a two-line improvement in Snellen visual acuity at the end of XO period for treatment of acute cystoid macular edema. There was a statistically significant benefit in using ophthalmic NSAIDs for chronic cystoid macular edema in two of the three studies for the improvement of visual acuity at the end of treatment (RR, 8.00; 95% CI, 1.16 to 55.20 and RR, 2.34; 95% CI, 1.25 to 4.40). There was a statistically significant benefit in using ophthalmic NSAIDs for chronic cystoid macular edema in one of the three studies for the improvement of visual acuity one month after treatment (RR, 3.37; 95% CI, 1.60 to 7.09). Secondary: Not reported
Intraoperative Miosis				
Roberts et al (abstract)[57] Diclofenac 0.1% one drop	AC, RCT Patients	N=51 1 day	Primary: Horizontal and vertical diameters of the pupil	Primary: There was no statistically significant difference between the two treatment groups in baseline pupil dilation (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
in the affected eye(s) every 15 minutes for four doses beginning one hour before surgery vs flurbiprofen 0.03% one drop in the affected eye(s) every 15 minutes for four doses beginning one hour before surgery Each patient also received dilating drops along with the study medication.	undergoing cataract extraction by phaco-emulsification		measured prior to initial conjunctival incision (baseline), every five minutes during the procedure, at the beginning of capsulorrhexis, the beginning of phaco-emulsification, the end of phacoemulsification, the end of cortical cleanup and before and after implantation of an IOL Secondary: Not reported	There were no statistically significant differences between the two treatment groups after start of surgery at any time point, except at the start of phacoemulsification, when the flurbiprofen group had more pupil dilation compared to the diclofenac group (P values not reported). Secondary: Not reported
Thaller et al (abstract)[58] Diclofenac 0.1% vs flurbiprofen 0.03% vs vehicle Each patient also received balanced salt solution containing adrenaline.	AC, DB, RCT Patients undergoing extracapsular cataract extraction with IOL implantation	N=52 Duration not specified	Primary: Change in pupil size (measured prior to the corneal section and after the completion of the operation), IOP, degree of inflammation (degree of pain, redness, flare and cells in the anterior chamber on day following surgery) Secondary: Not reported	Primary: There was a smaller decrease in pupil size in the diclofenac group compared to the flurbiprofen group (P values not reported). There was less postoperative redness reported in the diclofenac group compared to the other two groups (P=0.001). There were no significant differences between the three groups in terms of anterior chamber cells, flare or IOP change (P values not reported). Secondary: Not reported
Solomon et al[59] Flurbiprofen 0.03% one drop in the affected eye(s) every 15 minutes for three	AC, DB, PRO, RCT, SC Patients undergoing	N=118 1 day	Primary: Pupillary diameter measurements in the horizontal meridian at start of surgery, before	Primary: Mean horizontal papillary diameter measurements for the two treatment groups were similar at the start of surgery. There were measurably larger pupils in the ketorolac group compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
intervals beginning one hour prior to surgery vs ketorolac 0.5% one drop in the affected eye(s) every 15 minutes for three intervals beginning one hour prior to surgery	cataract extraction by phaco-emulsification with posterior chamber IOL implantation via scleral tunnel or clear corneal incision		phacoemulsification, before lens placement and following lens placement Secondary: Not reported	the flurbiprofen group; however, the difference was not statistically significant at the start of surgery (P=0.80), before phacoemulsification (P=0.27), before lens placement (P=0.26) or following lens placement (P=0.63). Patients receiving ketorolac had fewer miotic changes in the pre-phacoemulsification interval and greater mydriasis in the before and after lens placement intervals compared to patients receiving flurbiprofen; however, these differences were not statistically significant (P>0.05 for all intervals). Secondary: Not reported
Zanetti et al[60] Ketorolac 0.4% drops vs nepafenac 0.1% drops vs prednisolone acetate 1% drops vs placebo drops Each eye drop was administered TID for two days prior to surgery. Gatifloxacin was given	AC, DB, PC, PG, RCT Patients >50 years of age with nuclear cataract density of two and three by LOCS II with an indication for cataract surgery with intraocular lens implant	N=140 1 procedure (plus 2 days preop)	Primary: Number of patients with pupil ≥ 6mm (vertical and horizontal diameters) at the end of the surgery Secondary: Number of patients with pupil ≥ 6mm (vertical and horizontal diameters) at the beginning of the surgery (prior to the corneal section)	Primary: Baseline demographic and clinical characteristics were similar in all groups. There were no differences regarding ages (P=0.930), neither in age-related cataract density (P=0.852), nor in gender distribution (P=0.896), ultrasound time (P=0.986) and surgical time (P=0.666). All patients achieved pupil ≥ 6mm at the beginning of the surgery. The number of patients in prednisolone acetate (29/35), nepafenac (31/35) and ketorolac (30/35) groups with pupil ≥ 6mm was greater than the placebo group in the maintenance of intraoperative mydriasis at the conclusion of surgery (19/35) (P=0.003). There were no complications during surgery or related to the preoperative use of the eye drops. Secondary: There was a statistically significant difference in favor of preoperative use of topical anti-inflammatory agent on the maintenance of intraoperative mydriasis during cataract surgery compared to placebo (P<0.003). There was no statistical difference among the prednisolone, nepafenac and ketorolac groups in the maintenance of intraoperative mydriasis (P=0.791).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QID for two days prior to surgery with at least 15 minutes between two eye drops.				
Seasonal Allergic Conjunctivitis				
Tauber et al[61] Diclofenac 0.1% one drop in each eye QID vs ketorolac 0.5% one drop in each eye QID	AC, DB, MC, PG, PRO, RCT Patients with acute seasonal allergic conjunctivitis	N=60 14 days	Primary: Itching and bulbar conjunctival injection at 30 minutes, seven days and 14 days Secondary: Patient and physician's global improvement assessment with calculation of primary composite score (sum of scores for ocular itching and bulbar conjunctival injection) and a secondary composite score (sum of remaining sign and symptom scores), safety parameters including visual acuity, intraocular pressure and adverse events	Primary: Statistically significant improvements from baseline were observed for primary and secondary composite scores for both treatment groups at 30 minutes, seven days and 14 days compared to baseline (P<0.001 for all). Significant improvements for individual ocular itching and bulbar conjunctival injection occurred with both treatments compared to baseline (P<0.001 for all). Secondary: There were no statistically significant differences between the two treatment groups for the primary and secondary composite scores or for the individual parameters of itching and bulbar conjunctival injection. Treatment group differences were observed for pain/soreness score with an advantage observed for the diclofenac group at 30 minutes and day seven (P=0.007 and P=0.039, respectively). Significantly more patients in the diclofenac treatment group were free of symptoms at day seven compared to the treatment ketorolac group (20.7 vs 3.2%; P=0.049). There was no significant difference observed at day 14 visit with regard to the proportions of symptom-free patients in each treatment group (P value not reported). There were no significant changes in visual acuity or IOP throughout the evaluation period (P values not reported). No serious adverse events were reported in either treatment group. Minor adverse events included burning and stinging on instillation of the medication, burning/stinging, irritation, discharge. There was one instance of corneal erosion in the diclofenac group, which was attributed to eye rubbing due to itching.
Yaylali et al[62]	AC, PC, PG, RCT,	N=40	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Olopatadine 0.1% in one eye twice daily and placebo in the other eye twice daily vs ketorolac 0.5% in one eye four times daily and placebo in the other eye four times daily	SC Patients with SAC	15 days	Hyperemia and itching at 30 minutes then at two, seven and 15 days Secondary: Not reported	Hyperemia and itching were significantly improved in eyes treated with olopatadine and ketorolac compared to eyes treated with placebo at all time points (P<0.05 for all). The mean hyperemia score was lower in the olopatadine group compared to the ketorolac group; however, the difference was not statistically significant. The mean itching score was significantly lower in the olopatadine group compared to the ketorolac group from day two through to the end of the study (P<0.05). Secondary: Not reported
Discepola et al[63] Emedastine 0.05% in one eye and placebo in other eye once vs ketorolac 0.5% in one eye and placebo in the other eye once Patients received the alternate treatment in one eye and placebo in the contralateral eye at day 14.	AC, DB, PC, RCT, SC, XO Patients with a history of allergic conjunctivitis, study used CAC model	N=36 4 weeks	Primary: Ocular itching and redness at three, 10 and 20 minutes following CAC and ocular discomfort Secondary: Not reported	Primary: Emedastine significantly inhibited ocular itching and redness in vascular beds compared to placebo (P<0.05). Ketorolac failed to significantly inhibit ocular itching or redness compared to placebo (P value not reported). Patient assessment of comfort indicated emedastine was significantly more comfortable compared to ketorolac upon topical ocular administration (P<0.05). Secondary: Not reported
Shulman et al[64] Study 1 (n=45): cromolyn 4% vs pemirolast 0.1% vs ketorolac 0.5% given bilaterally one time only (3 visits XO)	DB, PG, PRO, RCT, SC Healthy adult volunteers, mean age 36 years in Study 1 and 34	N=93 Study 1: 7 days (3 visits) Study 2: 1 day	Primary: Overall ocular discomfort Secondary: Ocular burning/stinging, foreign-body sensation, tearing, photophobia,	Primary: Overall ocular discomfort was significantly lower with pemirolast than cromolyn (P=0.001), ketorolac (P<0.001), and nedocromil (P<0.001). Secondary: Burning/stinging and tearing were significantly lower with pemirolast than cromolyn and nedocromil (all P<0.05). Foreign body sensation was also

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Study 2 (n=48): nedocromil 2% vs pemirolast 0.1% given contralaterally one time only (1 visit)	years in Study 2		tolerability	significantly lower with pemirolast than nedocromil (P<0.05). There were no significant differences in photophobia between treatment groups. No notable differences were found in the incidence of adverse events between treatment groups (P values not reported).

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, PM=evening, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, IOP=intraocular pressure, MC=multicenter, NSAID=nonsteroidal anti-inflammatory drug, OL=open label, OS=observational study, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single blind, SC=single center, SR=systematic review, XO=cross over
Miscellaneous abbreviations: CME=cystoid macular edema, CMT=central macular thickness, IOL=intraocular lens, LOCS=Lens opacities classification system, Nd:YAG=neodymium-doped yttrium aluminum garnet, OCGA=ocular comfort grading assessment, OCT=optical coherence tomography, PGE_2=prostaglandin E_2, PH/MS=photon count per millisecond, SD=standard deviation, SOIS=summed ocular inflammation score, VAS=visual analog scale

Special Populations

Table 4. Special Populations[1-10]

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Bromfenac sodium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy have not been established in patients <18 years of age.	Not reported	Not reported	C*	Unknown; use caution.
Diclofenac sodium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy have not been established in pediatric patients.	Not reported	Not reported	C*	Unknown; use caution.
Flurbiprofen sodium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy have not been established in pediatric patients.	Not reported	Not reported	C*	Unknown; use caution.
Ketorolac tromethamine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy have not been established in patients <2 (0.5%) or <3 (0.4%) years of age. Safety and efficacy have not been established in patients <18 (0.45%) years of age.	Not reported	Not reported	C*	Unknown; use caution.
Nepafenac	No evidence of overall	Not reported	Not reported	C*	Unknown;

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy have not been established in patients <10 years of age.				use caution.

*Use during late pregnancy should be avoided because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus).

Adverse Drug Events

Table 5. Adverse Drug Events (%)[1-10,16]

Adverse Event(s)	Bromfenac Sodium	Diclofenac Sodium	Flurbiprofen Sodium	Ketorolac Tromethamine	Nepafenac
Cardiovascular					
Facial edema	-	≤3	-	-	-
Hypertension	-	-	-	-	1 to 4
Central Nervous System					
Fever	-	≤3	-	-	-
Headache	2 to 7	≤3	-	a *, 1 to 5†, 1 to 6‡	1 to 4
Insomnia	-	≤3	-	-	-
Pain	-	≤3	-	-	-
Gastrointestinal					
Abdominal pain	-	≤3	-	-	-
Nausea	-	≤3	-	-	1 to 4
Vomiting	-	≤3	-	-	1 to 4
Musculoskeletal					
Pain	-	≤3	-	-	-
Weakness	-	≤3	-	-	-
Ophthalmic					
Abnormal sensation	2 to 7	-	-	-	5 to 10
Abnormal vision	-	5	-	a *†, 1 to 6‡	5 to 10
Allergy	-	5	-	-	-
Bleeding of ocular tissues during ocular surgery	-	-	a	-	-
Blurred vision	3 to 8§	-	-	-	-
Capsular opacity	-	-	-	-	5 to 10
Conjunctival edema	-	-	-	-	1 to 5
Conjunctival hyperemia	2 to 7	-	a	1 to 5†, 1 to 6‡	1 to 5
Conjunctivitis	-	5	-	-	-
Corneal deposits	-	5	-	1 to 5†	-
Corneal edema	-	5	-	1 to 10*†, 1 to 6‡	1 to 5
Corneal erosion	a	a	-	a	-
Corneal infiltrates	-	a	-	a *, 1 to 5†	-

Adverse Event(s)	Bromfenac Sodium	Diclofenac Sodium	Flurbiprofen Sodium	Ketorolac Tromethamine	Nepafenac
Corneal lesions	-	5	-	-	-
Corneal opacity	-	5	-	-	-
Corneal perforation	a	a	-	a	-
Corneal thinning	a	a	-	a	-
Corneal ulceration	-	a	-	a *	-
Discharge	-	5	-	-	-
Dry eye	-	-	-	a	1 to 5
Edema	-	-	-	1 to 5†	-
Epithelial breakdown	a	a	-	a	-
Eyelid swelling	-	5	-	-	-
Fibrosis	-	-	a	-	-
Hyphema	-	-	a	-	-
Infection	-	5	-	1 to 10	-
Inflammation	3 to 8§	-	-	1 to 10	-
Intraocular pressure increased	-	15	-	1 to 6‡	5 to 10
Iritis	2 to 7	5	-	1 to 10	-
Irritation	2 to 7	5	a	1 to 10	1 to 5
Keratitis	-	28	-	-	-
Lacrimation	-	30	-	1 to 6‡	1 to 5
Lid margin crusting	-	-	-	-	1 to 5
Miosis	-	-	a	-	-
Mydriasis	-	-	a	-	-
Pain	2 to 8	-	-	1 to 10†, 1 to 6‡	1 to 5
Photophobia	3 to 8§	-	-	-	1 to 5
Pruritus	2 to 7	5	a	-	1 to 5
Redness	2 to 7	-	-	-	-
Superficial keratitis	-	a	-	1 to 10	-
Transient burning/stinging	2 to 7	15	a	40*,‡, 20 to 40†	-
Vitreous detachment	-	-	-	-	1 to 5
Other					
Allergic reaction	-	-	-	1 to 10	1 to 10
Viral infection	-	≤3	-	-	-
Respiratory					
Asthma exacerbation	-	-	-	a *	-
Bronchospasm	-	-	-	a *	-
Rhinitis	-	≤3	-	-	-
Sinusitis	-	-	-	-	1 to 4

a Percent not specified.
-Not reported or incidence <1%.
*Ketorolac tromethamine 0.5%.
†Ketorolac tromethamine 0.4%.
‡Ketorolac tromethamine 0.45%.
§Bromfenac 0.07%.

Contraindications

Table 6. Contraindications[1-10]

Contraindication	Bromfenac Sodium	Diclofenac Sodium	Flurbiprofen Sodium	Ketorolac Tromethamine	Nepafenac
Hypersensitivity to any component of the product	-	a	a	a	a
Hypersensitivity to any nonsteroidal anti-inflammatory drug	-	-	-	-	a

Warnings/Precautions

Table 7. Warnings and Precautions[1-10]

Warning/Precaution	Bromfenac Sodium	Diclofenac Sodium	Flurbiprofen Sodium	Ketorolac Tromethamine	Nepafenac
Cross-sensitivity; caution should be used in patients who have exhibited sensitivity to acetylsalicylic acid, phenylacetic acid derivatives or other nonsteroidal anti-inflammatory drugs (NSAIDs)	a	a	a	a	-
Contact lenses; do not administer while wearing contact lenses	a	-	-	a	a
Corneal adverse events; post-marketing experience suggests that topical NSAID use for more than 24 hours prior to surgery or use beyond 14 days following surgery may increase the risk of corneal adverse events	-	a	-	a	a
Increased bleeding time; topically applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery due to interference with platelet aggregation	a	a	a	a	a
Keratitis and corneal reactions; use of topical NSAIDs may result in keratitis in susceptible	a	a	-	a	a

Warning/Precaution	Bromfenac Sodium	Diclofenac Sodium	Flurbiprofen Sodium	Ketorolac Tromethamine	Nepafenac
patients; continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation, which may be sight-threatening					
Slow or delayed healing; all topical NSAIDs may slow or delay healing	a	a	a	a	a
Sulfite allergic reaction; anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people have been reported	a	-	-	-	-

Drug Interactions

Due to limited systemic absorption with ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs), drug interactions with other topical ophthalmic agents and systemically absorbed agents have not been fully investigated. Although clinical and animal studies have revealed no interference, acetylcholine chloride and carbachol have reportedly been ineffective when used in patients treated with ophthalmic flurbiprofen sodium.[1-10]

Dosage and Administration

Some ophthalmic NSAIDs have been shown to be safe when administered with other ophthalmic agents. Ophthalmic formulations of bromfenac sodium, ketorolac tromethamine and nepafenac may be administered in conjunction with ophthalmic formulations of alpha-agonists, beta blockers, carbonic anhydrase inhibitors, cycloplegics and mydriatics. Ophthalmic ketorolac tromethamine may also be administered with ophthalmic antibiotics. For bromfenac sodium, ketorolac tromethamine, and nepafenac, if more than one ophthalmic agent is being used at the same time, wait five minutes before administering the second medication.[1-11]

Table 8. Dosing and Adminsitration[1-10]

Generic Name	Adult Dose	Pediatric Dose	Availability
Bromfenac sodium	Treatment of pain and inflammation associated with cataract surgery: Ophthalmic solution (0.09%, Bromday®): Instill one drop into affected eye(s) once daily, beginning one day prior to surgery, continued on the day of surgery and through the first 14 days following surgery Ophthalmic solution (0.07%, Prolensa®): Instill one drop into affected eye(s) once daily, beginning one day prior to surgery, continued	Safety and efficacy have not been established in patients <18 years of age.	Ophthalmic solution: 0.09% (1.7 mL, 2.5 mL, 5 mL) 0.07% (1.6 mL, 3 mL)

Generic Name	Adult Dose	Pediatric Dose	Availability
	on the day of surgery and through the first 14 days following surgery Ophthalmic solution (0.09%): Instill one drop into affected eye(s) twice daily, beginning 24 hours after surgery, continued through the first 14 days following surgery		
Diclofenac sodium	Treatment of postoperative inflammation in patients who have undergone cataract extraction: Ophthalmic solution: Instill one drop into affected eye(s) four times daily, beginning 24 hours after surgery, continued through the first 14 days following surgery Temporary relief of pain and photophobia in patients undergoing corneal refractive surgery: Ophthalmic solution: Instill one or two drops into affected eye(s) within one hour prior to surgery, then one or two drops within 15 minutes after surgery, followed by one to two drops four times daily for up to three days	Safety and efficacy have not been established in patients <18 years of age.	Ophthalmic solution: 0.1% (2.5 mL, 5 mL)
Flurbiprofen sodium	Inhibition of intraoperative miosis: Ophthalmic solution: Instill one drop into affected eye(s) every 30 minutes for a total of four drops beginning two hours prior to surgery	Safety and efficacy have not been established in patients <18 years of age.	Ophthalmic solution: 0.03% (2.5 mL)
Ketorolac tromethamine	Treatment of pain and inflammation associated with cataract surgery: Ophthalmic solution (0.45%): Instill one drop into affected eye(s) twice daily, beginning 24 hours prior to surgery, continued on the day of surgery and through the first 14 days following surgery Treatment of postoperative inflammation in patients who have undergone cataract extraction: Ophthalmic solution (0.5%): Instill one drop into affected eye(s) four times daily, beginning 24 hours after cataract surgery, continued through the first 14 days following surgery Reduction of ocular pain and burning/stinging following corneal refractive surgery: Ophthalmic solution (0.4%): Instill one drop into affected eye(s) four times daily as needed for up to four days following surgery Temporary relief of ocular itching due to seasonal allergic conjunctivitis: Ophthalmic solution (0.5%): Instill one drop into	Safety and efficacy have not been established in patients <2 (0.5%) or <3 (0.4%) or <18 (0.45%) years of age.	Ophthalmic solution: 0.4% (5 mL) 0.45% (0.4 mL single-use vials in package of 30) 0.5% (3 mL, 5 mL, 10 mL)

Generic Name	Adult Dose	Pediatric Dose	Availability
	affected eye(s) four times daily		
Nepafenac	Treatment of pain and inflammation associated with cataract surgery: Ophthalmic suspension (0.1%): Instill one drop into affected eye(s) three times daily, beginning 24 hours prior to surgery, continued on the day of surgery and through the first 14 days following surgery Ophthalmic suspension (0.3%): Instill one drop into affected eye(s) once daily, beginning 24 hours prior to surgery, continued on the day of surgery and through the first 14 days following surgery. An additional drop should be administered 30 to 120 minutes prior to surgery.	Safety and efficacy have not been established in patients <10 years of age.	Ophthalmic suspension: 0.1% (3 mL) 0.3% (1.7 mL, 3 mL)

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Ophthalmology: **Preferred Practice Pattern: Cataract in the Adult Eye (2011)**[17]	Infection prophylaxis · Two emerging concerns are the increasing resistance of *Staphylococcus* species (the most common cause of endophthalmitis) to a broad spectrum of antibiotics, including the latest generation fluoroquinolones, and the increased occurrence of acute endophthalmitis more than a week after surgery. · Prophylactic strategies that have been used include applying topical antibiotic eye drops before surgery, applying 5% povidone iodine to the conjunctival cul de sac, preparing the periocular skin with 10% povidone iodine, careful sterile draping of the eyelid margins and eyelashes, adding antibiotics to the irrigating solution, instilling intracameral antibiotics at the close of surgery, injecting subconjunctival antibiotics and applying topical antibiotic eye drops after surgery. · Because of the lack of and impracticality of sufficiently large prospective clinical trials, there is insufficient evidence to recommend a specific antibiotic drug or method of delivery for endophthalmitis prophylaxis. · Systemic antibiotics are rarely used; however, it has been shown that certain oral fluoroquinolone antibiotics penetrate the blood/ocular barrier adequately to reach levels above the minimum inhibitory concentrations for many organisms inside the eye, and oral antibiotics that penetrate well into the eye may be beneficial. Postoperative follow-up · Postoperative regimens of topically applied antibiotics, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) vary among practitioners. · No controlled investigations establish optimal regimens for the use of topical agents. · The operating surgeon is responsible for making the decision whether

Clinical Guideline	Recommendations
	to use any or all of the topical products singly or in combination. · Complications of postoperative medications include elevated intraocular pressure with corticosteroids and allergic reactions to antibiotics. Significant corneal reactions, including epithelial defects and stromal ulceration and melting, have rarely been reported with topical NSAIDs. <u>Cystoid macular edema</u> · Topical anti-inflammatory agents are used in an attempt to reduce the inflammatory response to cataract surgery and to treat established cystoid macular edema. · There is evidence that topically applied NSAIDs alone or in combination with corticosteroids is more effective than topical corticosteroids alone in preventing and treating cystoid macular edema.
American Optometric Association: **Care of the Adult Patient with Cataract (2004)**[18]	· A combination of topical and oral anti-glaucoma, antibiotic and anti-inflammatory medications may be administered to the patient before, during and after an operation. · Topical corticosteroids may be used to suppress inflammation associated with cataract surgery. · To control inflammation associated with anterior uveitis, topical corticosteroids such as prednisolone acetate 1% may be used every two to four hours depending on the degree of inflammation.
American Academy of Ophthalmology: **Preferred Practice Pattern: Refractive Errors and Refractive Surgery (2013)**[19]	<u>Surface Ablation Techniques</u> · For photorefractive keratectomy, a topical antibiotic or antiseptic may be applied preoperatively to the operative eye, and a topical NSAID drop may also be applied to help ameliorate postoperative pain. · Postoperative topical antibiotics are administered to minimize the risk of infection. · Topical corticosteroids are generally started immediately after surgery and tapered over a period of days to weeks, and sometimes months. If corticosteroid treatment is prolonged, the intraocular pressure should be monitored. · Although postoperative pain may be reduced by the use of a bandage, contact lens and NSAID drops, patients may still require prescription oral analgesics. · Since NSAID drops may delay corneal epithelialization, they should be applied judiciously. · Sterile corneal infiltrates associated with the use of NSAID drops without the concomitant use of topical corticosteroids have been described. · Periodic examinations are necessary to monitor ocular status and to check for corticosteroid-related side effects such as elevated intraocular pressure. <u>Laser in Situ Keratomileusis</u> · A topical antibiotic or antiseptic may be applied preoperatively to the operative eye, and a topical NSAID eyedrop may also be applied to help ameliorate postoperative pain · Postoperative topical antibiotics are administered to minimize the risk of infection. · Corticosteroids are generally used for a short time postoperatively.

Clinical Guideline	Recommendations
	· Frequent lubrication is recommended in the postoperative period. · Symptoms of post-laser in situ keratomileusis epitheliopathy (reduced best corrected visual acuity, fluctuating vision, foreign-body sensation and discomfort) typically improve with time, but in certain cases they may persist for months or years. Supplemental lubrication, topical cyclosporine eye drops and punctal occlusion may be helpful in such cases. · Diffuse lamellar keratitis is a noninfectious aggregation of inflammatory cells, and treatment is commonly guided by the severity of the inflammation. Increasing the frequency of topical corticosteroid administration with a closer follow-up is practiced by most surgeons.
American Academy of Ophthalmology: **Preferred Practice Pattern: Conjunctivitis (2013)**[20]	<u>Seasonal allergic conjunctivitis</u> · Treatment of conjunctivitis is ideally directed at the root cause. Indiscriminate use of topical antibiotics or corticosteroids should be avoided because antibiotics can induce toxicity, and corticosteroids can potentially prolong adenoviral infections and worsen herpes simplex virus infections. · Treat mild allergic conjunctivitis with an over-the-counter (OTC) antihistamine/vasoconstrictor or second-generation topical histamine H_1-receptor antagonist. The guideline does not give preference to one OTC antihistamine/vasoconstrictor or antihistamine vs another. The guideline does not address the role of prescription vasoconstrictors in the management of allergic conjunctivitis. · If the condition is frequently recurrent or persistent, use mast-cell stabilizers. The guideline does not give preference to one mast-cell stabilizer vs another. · Medications with antihistamine and mast-cell stabilizing properties may be utilized for either acute or chronic disease. The guideline does not give preference to one antihistamine/mast-cell stabilizer vs another. · If the symptoms are not adequately controlled, a brief course (one to two weeks) of low-potency topical corticosteroid may be added to the regimen. The lowest potency and frequency of corticosteroid administration that relieves the patient's symptoms should be used. · Ketorolac, an NSAID, is also Food and Drug Administration (FDA)-approved for the treatment of allergic conjunctivitis. · Additional measures include allergen avoidance and using cool compresses, oral antihistamines and artificial tears, which dilute allergens and treat coexisting tear deficiency. Frequent clothes washing and bathing before bedtime may also be helpful. · Consultation with an allergist or dermatologist may be helpful for patients with disease that cannot be adequately controlled with topical medications and oral antihistamines. <u>Vernal/atopic conjunctivitis</u> · General treatment measures include modifying the environment to minimize exposure to allergens or irritants and using cool compresses and ocular lubricants. Topical and oral antihistamines and topical mast-cell stabilizers may be beneficial in maintaining comfort. · For acute exacerbations, topical corticosteroids are usually necessary to control severe symptoms. The minimal amount of corticosteroid should be used based on patient response and tolerance. Topical cyclosporine is effective as adjunctive therapy to reduce the amount of

Clinical Guideline	Recommendations
	topical corticosteroid used to treat severe atopic keratoconjunctivitis. For entities such as vernal keratoconjunctivitis, which may require repeat short-term therapy with topical corticosteroid, patients should be informed about potential complications of corticosteroid therapy, and general strategies to minimize corticosteroid use should be discussed. · For severe sight-threatening atopic keratoconjunctivitis that is not responsive to topical therapy, supratarsal injection of corticosteroid can be considered. · Systemic immunosuppression may rarely be warranted. · In patients two years of age or older, eyelid involvement may be treated with pimecrolimus cream or tacrolimus ointment. Patients should be told to keep these medications away from the conjunctival and corneal surface and from the tear film. Both agents are rarely associated with the development of skin cancer and lymphoma. · Frequency of follow-up visits is based on the severity of disease presentation, etiology and treatment. Consultation with a dermatologist is often helpful. If corticosteroids are prescribed, baseline and periodic measurement of intraocular pressure and papillary dilation should be performed to evaluate for glaucoma and cataract(s). <u>Mild bacterial conjunctivitis</u> · Mild bacterial conjunctivitis may be self-limited and resolve spontaneously without treatment in immunocompetent adults. · Ophthalmic antibacterial therapy is associated with earlier clinical and microbiological remission compared to placebo at days two to five of treatment. The advantages persist over six to 10 days, but the benefit over placebo lessens over time. · The choice of ophthalmic antibiotic is usually empirical. · A five to seven day course of ophthalmic broad-spectrum antibiotic is usually effective. · The most convenient or least expensive option can be selected. <u>Severe bacterial conjunctivitis</u> · Severe bacterial conjunctivitis is characterized by copious purulent discharge, pain and marked inflammation of the eye. · The choice of ophthalmic antibiotic is guided by the results of laboratory tests. · Methicillin-resistant *Staphylococcus aureus* (MRSA) has been isolated with increasing frequency from patients with bacterial conjunctivitis. Many MRSA organisms are resistant to commercially available ophthalmic antibiotics. · Systemic antibiotic therapy is necessary to treat conjunctivitis due to *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. · If corneal involvement is present, the patient should also be treated topically for bacterial keratitis. <u>Herpes simplex virus conjunctivitis</u> · Topical and/or oral antiviral treatment is recommended for herpes simple virus conjunctivitis to prevent corneal infection. · Possible options include topical ganciclovir 0.15% gel applied three to fiv times per day, trifluridine 1% solution applied five to eight times per day, or oral acyclovir 200 to 400 mg administered five times per day.

Clinical Guideline	Recommendations
	· Oral valacyclovir and famciclovir also can be used. · Topical antiviral agents may cause toxicity if used for more than two weeks. · Topical corticosteroids potentiate herpes simplex virus infection and should be avoided. · Follow-up care management within one week of treatment is advised and should include an interval history, visual acuity measurement, and slit-lamp biomicroscopy. · Neonates require prompt consultation with the pediatrician or primary care physician, because systemic herpes simplex virus infection is a life-threatening condition.
American Optometric Association: **Optometric Clinical Practice Guideline: Care of the Patient With Conjunctivitis (2007)**[21]	Allergic conjunctivitis (includes atopic keratoconjunctivitis, simple allergic conjunctivitis, seasonal or perennial conjunctivitis and vernal conjunctivitis) · The treatment of allergic conjunctivitis is based upon identification of specific antigens and elimination of specific pathogens, when practical, and upon the use of medications that decrease or mediate the immune response. The use of supportive treatment, including unpreserved lubricants and cold compresses, may provide symptomatic relief. · The following agents are useful in treating allergic conjunctivitis: topical corticosteroids (numerous products listed), vasoconstrictors/antihistamines (specific products not listed), antihistamines (azelastine, emedastine and levocabastine*), NSAIDs (ketorolac), mast cell stabilizers (cromolyn, lodoxamide, nedocromil and pemirolast), antihistamines/mast cell stabilizers (ketotifen and olopatadine) and immunosuppressants; and systemic immunosuppressants and antihistamines. · Topical corticosteroids are effective in relieving the acute symptoms of allergy; however, their use should be limited to the acute suppression of symptoms because of the potential for adverse side effects with prolonged use (e.g., cataract formation and elevated intraocular pressure). · Topical vasoconstrictors/antihistamines cause vascular constriction, decrease vascular permeability and reduce ocular itching by blocking histamine H_1 receptors. The guideline does not address the role of prescription vasoconstrictors in the management of allergic conjunctivitis. · Topical antihistamines competitively bind with histamine receptor sites and reduce itching and vasodilation. Azelastine, emedastine and levocabastine* are effective in reducing the symptoms of allergic conjunctivitis, and emedastine may be more efficacious than levocabastine*. · Topical diclofenac and ketorolac, which are both NSAIDS, are effective in reducing the signs and symptoms associated with allergic conjunctivitis, although only ketorolac is FDA approved for this indication. · Nedocromil, an effective treatment for seasonal allergic conjunctivitis, is more effective than cromolyn (2%†) in treating vernal conjunctivitis. Nedocromil was less effective than fluorometholone in treating severe vernal keratoconjunctivitis but has fewer side effects. Lodoxamide has demonstrated a greater improvement in the signs and symptoms of allergic eye disease, including vernal keratoconjunctivitis, than cromolyn (2† or 4%). Pemirolast has FDA approval as a treatment to relieve (to prevent) itching associated with allergic conjunctivitis.

Clinical Guideline	Recommendations
	· Ketotifen and olopatadine are selective histamine H_1-receptor antagonists that also have mast cell stabilizing properties. Olopatadine may be more effective than other mast cell stabilizing agents in targeting the subtype of mast cell found in the conjunctiva. Compared to ketorolac or ketotifen, olopatadine is more effective in relieving the itching and redness associated with acute allergic conjunctivitis. · Systemically administered cyclosporine may be an effective treatment for patients with severe atopic keratoconjunctivitis. Topical cyclosporine is an alternative to topical corticosteroids for treatment of patients with severe atopic keratoconjunctivitis. Topical cyclosporine may also be beneficial in patients with vernal keratoconjunctivitis who have failed conventional therapy. · Systemic antihistamines are useful when the allergic response is associated with lid edema, dermatitis, rhinitis or sinusitis. They should be used with caution because of the sedating and anticholinergic effects of some first-generation antihistamines. Newer antihistamines are much less likely to cause sedation, but their use may result in increased ocular surface dryness. Viral conjunctivitis · Most viral conjunctivitis is related to adenoviral infection; however, no antiviral agent has been demonstrated to be effective in treating these infections. · Topical NSAID therapies have shown no benefit in reducing viral replication, decreasing the incidence of sub-epithelial infiltrates, or alleviating symptoms. · Topical antibiotics are not routinely used to treat viral conjunctivitis, unless there is evidence of secondary bacterial infection. · The treatment of herpes simplex conjunctivitis may include the use of antiviral agents such as trifluridine, although there is no evidence that this therapy results in a lower incidence of recurrent disease or keratitis. · Supportive therapy, including lubricants and cold compresses, which may be as effective as antiviral drugs, eliminates the potential for toxic side effects. · Topical steroids are specifically contraindicated for treating herpes simplex conjunctivitis.

*Product is not available in the United States.
†Cromolyn 4% but not 2% is available in the United States. The concentrations of cromolyn that were used in the original clinical studies are noted in this table.

Conclusions

The currently available ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) include bromfenac sodium (Bromday®, Prolensa®, generic), diclofenac sodium, flurbiprofen sodium (Ocufen®), ketorolac tromethamine (Acular®, Acular LS®, Acuvail®) and nepafenac (Nevanac®, Ilevro®).[1-11] The ophthalmic NSAIDs exert their anti-inflammatory activity primarily by nonselective inhibition of cyclooxygenase-1 and cyclooxygenase-2 enzymes. These agents are Food and Drug Administration (FDA)-approved for various non-infectious ocular conditions including management of pain and inflammation following cataract and corneal refractive surgeries, inhibition of intraoperative miosis and relief of ocular itching due to seasonal allergic conjunctivitis. Ophthalmic formulations of bromfenac sodium, diclofenac sodium, flurbiprofen sodium and ketorolac tromethamine 0.4% and 0.5% are available generically. Ophthalmic formulations of diclofenac sodium and ketorolac tromethamine 0.45% are the only ophthalmic NSAIDs that are formulated as preservative-free.[1-10]

The ophthalmic NSAIDs have been shown to be safe and effective in inhibiting intraoperative miosis, reducing postoperative inflammation and pain associated with cataract surgery, relieving pain and photophobia following corneal refractive surgery and relieving seasonal allergic conjunctivitis symptoms in placebo-controlled trials. Although not FDA-approved, there is evidence to support the use of ophthalmic NSAIDs for preventing or treating cystoid macular edema and for reducing pain associated with various other refractive surgeries.[50-55] The results of head-to-head trials comparing ophthalmic NSAIDs have not consistently demonstrated any one agent to be more efficacious than another for a given indication.[31-32,34,35,48,50,51,56,57,60] With regard to safety, not one agent was consistently reported to be better tolerated than another across trials, although there is some evidence that the preservative-free products may be associated with less ocular irritation.[45] Corneal complications have been reported to occur with all of the agents in the class and the risk does not appear to be higher with one agent compared to another. Consensus guidelines established by the American Academy of Ophthalmology and the American Optometric Association recommend the use of topical NSAIDs for preventing and treating cystoid macular edema due to cataract surgery. Available evidence suggests that ophthalmic NSAIDs either alone or in combination with ophthalmic corticosteroids are more effective than ophthalmic corticosteroids alone. The ophthalmic NSAIDs are not associated with an increase in intraocular pressure, which may occur with the use of corticosteroids.[17,18]

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