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What is The Comparative Effectiveness of Different Pharmacological Interventions in Preventing Cystoid Macular Edema after Cataract Surgery in Nondiabetic versus Diabetic Patients? : A Systematic Review

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Abstract: Introduction: Cystoid macular edema (CME) is a common vision-impairing complication following cataract surgery, with diabetic patients exhibiting a higher predisposition due to pre-existing retinal microvascular changes. This systematic review evaluates the comparative effectiveness of pharmacological interventions—nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and anti-vascular endothelial growth factor (anti-VEGF) agents—in preventing CME in nondiabetic versus diabetic patients.
Methods: Adhering to PRISMA 2020 guidelines, this systematic review included randomized controlled trials, systematic reviews, and meta-analyses that assessed pharmacological CME prevention in adult cataract surgery patients, differentiated by diabetic status. Searched databases included PubMed, Semantic Scholar, Sagepub, and Google Scholar. Primary outcomes analyzed were CME incidence, central retinal thickness (CRT) measured by optical coherence tomography (OCT), and best-corrected visual acuity (BCVA).
Results: In nondiabetic patients, NSAIDs, alone or combined with corticosteroids, demonstrated superior efficacy in reducing CME incidence (e.g., 1.5% with bromfenac/dexamethasone combination vs. 5.1% with dexamethasone alone) and stabilizing CRT compared to corticosteroid monotherapy or placebo. For diabetic patients, NSAIDs, corticosteroids, and anti-VEGF agents all contributed to lower CME incidence (e.g., ranibizumab reducing rates from 17.1% to 2.7%) and reduced CRT. Visual acuity outcomes generally improved with active interventions in both groups, though some studies reported no significant differences. Interventions were generally well-tolerated; corticosteroids posed a risk of increased intraocular pressure, particularly in diabetics.
Discussion: The evidence supports NSAIDs as a cornerstone for CME prophylaxis in nondiabetic patients by mitigating postoperative inflammation. Diabetic patients, with their compromised retinal vasculature, benefit from a broader pharmacological spectrum, including anti-VEGF agents that target VEGF-mediated permeability. Combination therapies often yield the most significant protective effects.

Conclusion: Pharmacological interventions are effective in preventing post-cataract surgery CME. NSAIDs, alone or with corticosteroids, are recommended for nondiabetic patients. A multimodal approach, potentially incorporating NSAIDs, corticosteroids, and anti-VEGF agents, is advisable for diabetic patients, tailored to individual risk profiles.

Keywords: Cystoid Macular Edema, Cataract Surgery, Diabetic Patients, Nondiabetic Patients, Pharmacological Interventions, NSAIDs, Corticosteroids, Anti-VEGF, Central Retinal Thickness, Visual Acuity.

INTRODUCTION

Cystoid macular edema (CME) is a significant postoperative complication following cataract surgery, characterized by the accumulation of fluid in the macula leading to vision impairment. The prevention of CME is critical, especially in vulnerable populations such as diabetic patients, who exhibit a higher baseline risk due to pre-existing microvascular retinal changes (Howaidy et al., 2021). Various pharmacological interventions have been investigated to mitigate this risk, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and anti-vascular endothelial growth factor (anti-VEGF) agents.

Optical coherence tomography (OCT), particularly spectral domain OCT (SD-OCT), plays a pivotal role in diagnosing and monitoring CME by providing precise measurements of central macular thickness and detecting subtle structural changes before clinical symptoms arise (Wielders et al., 2018). This imaging modality allows for objective assessment of treatment efficacy in clinical trials and routine practice (Howaidy et al., 2021).

In nondiabetic populations, NSAIDs alone or in combination with corticosteroids have demonstrated superior efficacy in reducing CME incidence compared to corticosteroid monotherapy or placebo. For instance, bromfenac and dexamethasone combinations have resulted in CME incidences as low as 1.5% to 3.6%, with corresponding central macular thickness values between 284.5 and 296.0 microns (Wielders et al., 2018; Mamalis, 2018). These findings suggest that NSAIDs effectively reduce postoperative inflammation, a key factor in CME pathogenesis.

Diabetic patients, due to their compromised retinal vasculature, benefit from a broader range of pharmacological agents. Studies report that NSAIDs, corticosteroids, and anti-VEGF agents all contribute to lowering CME incidence and central retinal thickness. Notably, ranibizumab and bevacizumab have shown significant reduction in CME rates, with incidences dropping from 17.1% in untreated eyes to as low as 2.7% and 5%, respectively (Howaidy et al., 2021; Elsadi et al., 2021). These agents target VEGF-mediated vascular permeability, which is heightened in diabetic retinopathy.

Visual acuity outcomes, an essential functional measure, generally improve with pharmacological prophylaxis. Several studies have documented better best-corrected visual acuity (BCVA) in patients receiving NSAIDs or anti-VEGF agents compared to controls (Alnagdy et al., 2018; Zhang et al., 2022). However, some trials report no significant difference, highlighting the need for individualized treatment considerations based on patient risk profiles (Mohammad-Rabei et al., 2023).

Safety profiles of these pharmacological interventions are favorable. NSAIDs are typically well tolerated with minimal adverse effects such as mild ocular irritation. Corticosteroids, while effective, carry a risk of increased intraocular pressure, necessitating careful monitoring, especially in diabetic patients (Wielders et al., 2018). Anti-VEGF agents have not demonstrated major safety concerns in the reviewed studies, supporting their use in high-risk cases (Howaidy et al., 2021).

The heterogeneity of study designs, including randomized controlled trials, meta-analyses, and systematic reviews, strengthens the evidence base for pharmacological prevention of CME. Multi-center trials and meta-analyses provide robust data supporting NSAIDs as first-line agents in nondiabetics and a combination approach

incorporating anti-VEGF therapy in diabetics (Laursen et al., 2019; Wielders et al., 2015).

Despite these advances, some studies report no significant differences between interventions and controls, indicating that CME pathophysiology is multifactorial and may require tailored prophylactic strategies. Further research is needed to optimize timing, dosing, and combinations of pharmacological agents to maximize efficacy and safety (Khodabandeh et al., 2018).

In summary, the prevention of CME after cataract surgery is essential to preserve visual function, with NSAIDs playing a central role in nondiabetic patients and a multimodal pharmacological approach benefiting diabetic patients. Advances in OCT technology have facilitated early detection and monitoring, enabling timely intervention and improved outcomes.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the comparative effectiveness of different pharmacological interventions in preventing cystoid macular edema after cataract surgery in nondiabetic versus diabetic patients.

Screening

We screened in papers that met these criteria:

- **Adult Population**: Does the study exclusively include adult patients (18 years) undergoing cataract surgery?
- **Intervention Type**: Does the study evaluate at least one pharmacological intervention for preventing cystoid macular edema?
- **Population Classification**: Does the study clearly differentiate between diabetic and nondiabetic patients in their analysis or focus exclusively on one of these populations?
- **Study Design**: Is the study design a randomized controlled trial, systematic review, or meta-analysis?
- **Outcome Measures**: Does the study report at least one of these outcomes: incidence of macular edema, severity, visual acuity, or time to development?
- **Diagnostic Methods**: Does the study use optical coherence tomography (OCT) or fluorescein angiography for diagnosis of macular edema?
- **Pre-existing Conditions**: Are all study participants free from pre-existing macular edema and major ocular comorbidities (such as uveitis or retinal vein occlusion)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- Study Design:

Identify the specific type of study design. Look in the methods section for precise description. Accept- able answers include:

- Randomized controlled trial (RCT)

- Prospective randomized controlled study
- Multicenter randomized trial

If multiple design descriptors are present, list all. If design is unclear, note ”design not clearly specified”. Specific details to extract:

- Whether randomization was used
- Whether the study was single-center or multi-center
- Prospective or retrospective nature of the study
- Participant Characteristics:

Extract detailed participant information from methods and participant flow sections:

- Total number of participants
- Number of participants in each study arm/group
- Specific inclusion criteria (e.g., diabetic patients, no preoperative macular edema)
- Mean age
- Gender distribution
- Specific diabetes-related characteristics (if applicable)

If any information is missing, note ”[data not reported]”. Use precise numerical values where possible.

- Intervention Details:

For each study group, extract:

- Specific pharmacological intervention (drug name, dosage)
- Route of administration (topical, intravitreal, subconjunctival)
- Timing of intervention (pre-operative, intra-operative, post-operative)
- Frequency of intervention
- Duration of intervention

If multiple interventions are used in combination, list all components. Be as precise as possible about dosages and timing.

- **Comparison/Control Conditions**:

Identify:

- What the control group received (placebo, standard care, no treatment)
- Specific details of control intervention
- Whether control group was truly comparable to intervention groups

If no clear control is specified, note ”No control group” or ”Control group not clearly defined”.

- Primary Outcome Measures:

Extract all primary outcome measures related to cystoid macular edema (CME), specifically:

- Method of measuring CME (e.g., SD-OCT, central macular thickness)
- Specific measurements (e.g., change in macular thickness in m)
- Time points of outcome measurement
- Statistical significance of results

Use exact numerical values and p-values when reported. If outcomes are not clearly specified, note ”[primary outcomes not clearly defined]”.

- **Secondary Outcome Measures**:
- Extract secondary outcomes such as:
- Visual acuity measurements

- Incidence of clinically significant macular edema
- Adverse events
- Intraocular pressure changes

Include specific numerical results, measurement methods, and statistical significance where reported.

- **Study Setting and Time Frame**:

Extract:

- Geographic location of study (countries/centers)
- Total study duration
- Follow-up period (e.g., 6 weeks, 12 weeks, 3 months)
- Specific time points of measurements

If any information is incomplete, note ”[data not fully reported]”.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Diabetic patients	Nondiabetic patients	Adult cataract surgery patients	Patients with/without diabetic retinopathy
Intervention (I)	Nonsteroidal anti-inflammatory drugs (NSAIDs)	Anti-vascular endothelial growth factor agents (anti-VEGF)	Corticosteroids	Combination therapy (NSAIDs + corticosteroids)
Comparison (C)	Placebo	No prophylaxis	Corticosteroid monotherapy	NSAIDs monotherapy
Outcome (O)	Incidence of cystoid macular edema	Central retinal thickness	Best-corrected visual acuity	Safety/adverse events

The Boolean MeSH keywords inputted on databases for this research are: *("Diabetic patients" OR "Nondiabetic patients" OR "Adult cataract surgery patients" OR "Patients with/without diabetic retinopathy") AND ("Nonsteroidal anti-inflammatory drugs" OR "Anti-vascular endothelial growth factor agents" OR "Corticosteroids" OR "Combination therapy") AND ("Placebo" OR "No prophylaxis" OR "Corticosteroid monotherapy" OR "NSAIDs monotherapy") AND ("Incidence of cystoid macular edema" OR "Central retinal thickness" OR "Best-corrected visual acuity" OR "Safety/adverse events")*

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Diabetic patients" OR "Nondiabetic patients" OR "Adult cataract surgery patients" OR "Patients with/without diabetic retinopathy") AND ("Nonsteroidal anti-inflammatory drugs" OR "Anti-vascular endothelial growth factor agents" OR "Corticosteroids" OR "Combination therapy") AND ("Placebo" OR "No prophylaxis" OR "Corticosteroid monotherapy" OR "NSAIDs monotherapy") AND ("Incidence of cystoid macular edema" OR "Central retinal thickness" OR "Best-corrected visual acuity" OR "Safety/adverse events")*	7
Semantic Scholar	*("Diabetic patients" OR "Nondiabetic patients" OR "Adult cataract surgery patients" OR "Patients with/without diabetic retinopathy") AND ("Nonsteroidal anti-inflammatory drugs" OR "Anti-vascular endothelial growth factor agents" OR "Corticosteroids" OR "Combination therapy") AND ("Placebo" OR "No prophylaxis" OR "Corticosteroid monotherapy" OR "NSAIDs monotherapy") AND ("Incidence of cystoid macular edema" OR "Central retinal thickness" OR "Best-corrected visual acuity" OR "Safety/adverse events")*	250
Sagepub	*("Diabetic patients" OR "Nondiabetic patients" OR "Adult cataract surgery patients" OR "Patients with/without diabetic retinopathy") AND ("Nonsteroidal anti-inflammatory drugs" OR "Anti-vascular endothelial growth factor agents" OR "Corticosteroids" OR "Combination therapy") AND ("Placebo" OR "No prophylaxis" OR "Corticosteroid monotherapy" OR "NSAIDs monotherapy") AND ("Incidence of cystoid macular edema" OR "Central retinal thickness" OR "Best-corrected visual acuity" OR "Safety/adverse events")*	7,905
Google Scholar	*("Diabetic patients" OR "Nondiabetic patients" OR "Adult cataract surgery patients" OR "Patients with/without diabetic retinopathy") AND ("Nonsteroidal anti-inflammatory drugs" OR "Anti-vascular endothelial growth factor agents" OR "Corticosteroids" OR "Combination therapy") AND ("Placebo" OR "No prophylaxis" OR "Corticosteroid monotherapy" OR "NSAIDs monotherapy") AND ("Incidence of cystoid macular edema" OR "Central retinal thickness" OR "Best-corrected visual acuity" OR "Safety/adverse events")*	23,300

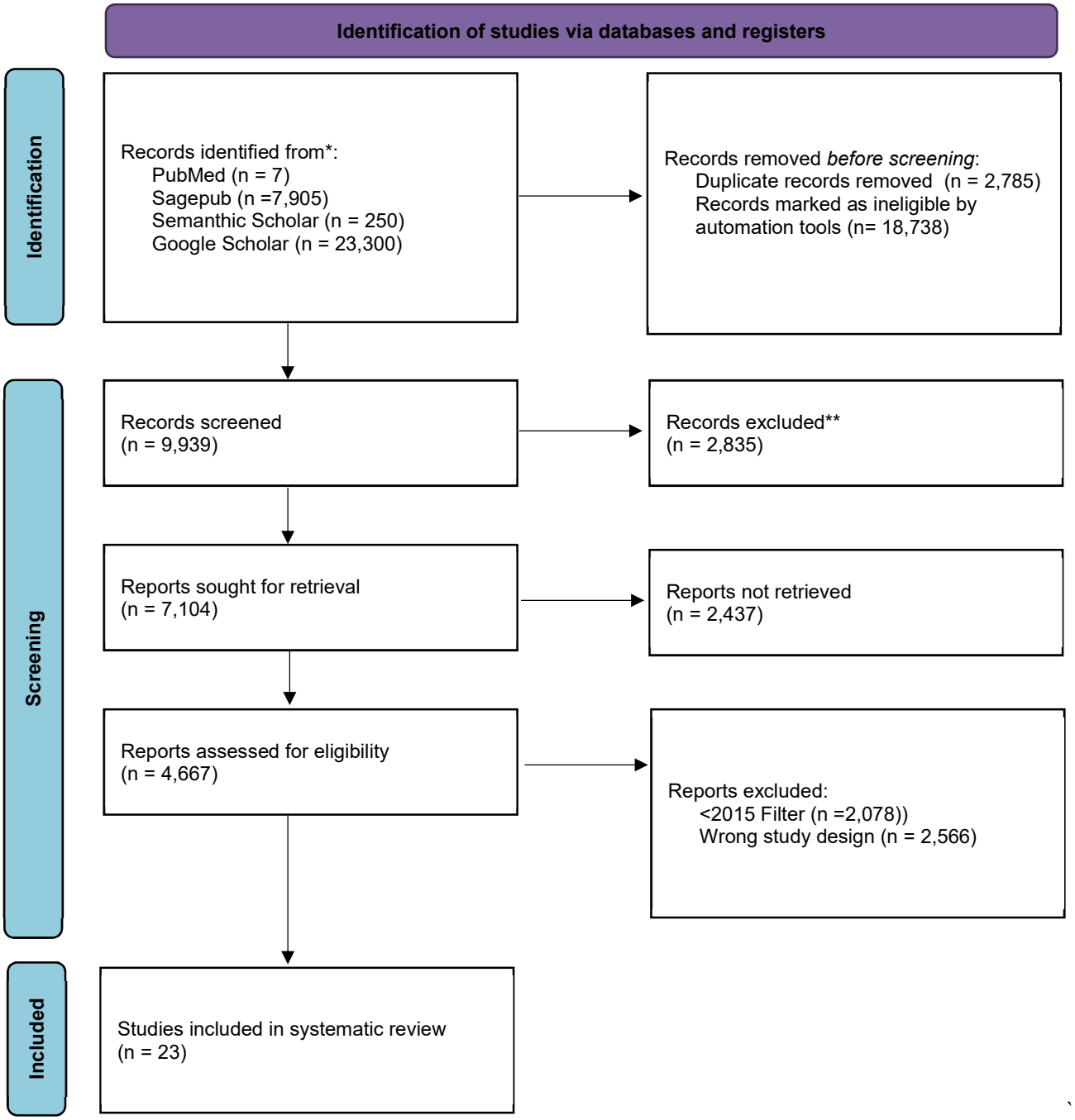

Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	**Bias related to tempor**	**Bias related to selection and**	**Bias related to confounding factors**	**Bias related to administration of**	**Were there multiple measure**	**Were the outcomes of participa**	**Were outcomes measur**	**Bias related to participa**	**Statistical conclusion validity**

	al precedence Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	**allocation** Was there a control group?	Were participants included in any comparisons similar?	**intervention/exposure** Were the participants included in any comparisons receiving similar treatment/ care, other than the exposure or intervention of interest?	**ments o the outcome, both pr and pos the interventi on/exposu re?**	**nts included in any comparisons measured in the same way?**	**ed in a reliable way?**	**nt retention** Was follow-up complete and, if not were differences between groups in terms o their follow-up adequately described and analyzed?	Was appropriat e statistica analysis used?
Howaidy et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Laursen et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wielders et al., 2018, "ESCRS PREMED Study Report 2"	✓	✓	✓	✗	✓	✗	✓	✓	✓
Khodabandeh et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wielders et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓

Wielders et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Wielders et al., 2018, "ESCRS PREMED Study Report 1"	✓	✓	✓	✗	✓	✗	✓	✓	✓
Zhang et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kim and Jampel, 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mamalis, 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Alnagdy et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mokbel et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ramakrishnan et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Nanji et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Kohnen, 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jung et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tzelikis et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
Campa et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓

Elsadi et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Duong et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jabeen and Raza, 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Mohammad-Rabei et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ilveskoski et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

Study	Study Design	Population Type	Intervention Type	Primary Outcomes	Full text Retrieved
Howaidy et al., 2021	Prospective randomized controlled trial	Diabetic, no preoperative diabetic macular edema	Nepafenac, ranibizumab, no prophylaxis	Central macular thickness (spectral domain optical coherence tomography), cystoid macular edema incidence,	No

				best-corrected visual acuity	
Laursen et al., 2019	Meta-analysis of randomized controlled trials	Diabetic	Topical corticosteroids with or without nonsteroidal anti-inflammatory drugs, depot corticosteroids, anti-vascular endothelial growth factor agents	Pseudophakic cystoid macular edema risk ratio, visual acuity, macular thickness	No
Wielders et al., 2018, "ESCRS PREMED Study Report 2"	Multicenter randomized controlled trial	Diabetic	Bromfenac plus dexamethasone with or without triamcinolone, bevacizumab	Central macular thickness, cystoid/clinically significant macular edema incidence, best-corrected visual acuity	No
Khodabandeh et al., 2018	Prospective randomized controlled trial	Diabetic, no/mild non-proliferative diabetic retinopathy	Phacoemulsification with or without intravitreal bevacizumab	Central macular thickness (spectral domain optical coherence tomography), best-corrected visual acuity, total macular volume	No
Wielders et	Systematic	Diabetic &	Nonsteroidal	Cystoid	No

al., 2015	review/meta-analysis	nondiabetic	anti-inflammatory drugs, corticosteroids, combinations, anti-vascular endothelial growth factor agents	macular edema odds, foveal thickness, macular volume, best-corrected visual acuity	
Wielders et al., 2017	Systematic review of randomized controlled trials	Diabetic & nondiabetic	Nonsteroidal anti-inflammatory drugs, corticosteroids, sub-Tenon, oral nonsteroidal anti-inflammatory drugs	Visual acuity, cystoid macular edema	No
Wielders et al., 2018, "ESCRS PREMED Study Report 1"	Multicenter randomized controlled trial	Nondiabetic	Bromfenac, dexamethasone, combination	Central macular thickness, cystoid/clinically significant macular edema incidence, best-corrected visual acuity	No
Zhang et al., 2022	Bayesian network meta-analysis	Diabetic	Anti-vascular endothelial growth factor agents, nonsteroidal anti-inflammatory drugs, corticosteroids	Postoperative macular edema risk, best-corrected visual acuity	No

Kim and Jampel, 2016	Systematic review/meta-analysis critique	Diabetic & nondiabetic	Not applicable	Critique of outcome definitions	No
Mamalis, 2018	Editorial review	Nondiabetic & diabetic	Nonsteroidal anti-inflammatory drugs, corticosteroids	Central macular thickness, cystoid/clinically significant macular edema incidence, best-corrected visual acuity	No
Alnagdy et al., 2018	Single-center randomized controlled trial	Diabetic	Nepafenac, ketorolac, placebo	Central macular thickness (optical coherence tomography), best-corrected visual acuity, cystoid macular edema incidence	Yes
Mokbel et al., 2019	Single-center randomized controlled trial	Diabetic	Nepafenac vs. no nepafenac	Foveal thickness (optical coherence tomography), cystoid macular edema incidence, best-corrected visual acuity	Yes

Ramakrishnan et al., 2015	Prospective randomized controlled trial	Low-risk (subgroup: diabetic)	Nepafenac vs. ketorolac	Central macular thickness (optical coherence tomography), subclinical cystoid macular edema	No
Nanji et al., 2024	Protocol for systematic review/network meta-analysis	Mixed	Nonsteroidal anti-inflammatory drugs, corticosteroids, various routes	Central macular thickness (optical coherence tomography), cystoid/clinically significant macular edema, best-corrected visual acuity, quality of life, intraocular pressure, adverse events	Yes
Kohnen, 2018	Editorial review	Diabetic	Triamcinolone, bevacizumab	Cystoid macular edema incidence, macular thickness, best-corrected visual acuity	No
Jung et al., 2015	Single-center randomized	Mixed (including diabetics)	Bromfenac, ketorolac, corticosteroid	Central macular thickness	Yes

	controlled trial			(optical coherence tomography), macular volume, best-corrected visual acuity	
Tzelikis et al., 2018	Prospective randomized controlled trial	Bilateral cataract	Nepafenac vs. placebo	Central macular thickness (spectral domain optical coherence tomography), cystoid macular edema incidence, best-corrected visual acuity	No
Campa et al., 2018	Prospective randomized controlled trial	Routine cataract	Dexamethasone alone, plus bromfenac, plus nepafenac	Cystoid macular edema incidence, central macular thickness (optical coherence tomography), best-corrected visual acuity	No
Elsadi et al., 2021	Prospective controlled	Diabetic	Phacoemulsification with or without intraoperative bevacizumab	Central macular thickness (optical coherence tomography),	No

				diabetic macular edema incidence, best-corrected visual acuity	
Duong et al., 2015	Prospective randomized controlled trial	Mixed	Bromfenac vs. prednisolone	Foveal thickness (optical coherence tomography), best-corrected visual acuity	No
Jabeen and Raza, 2019	Randomized controlled trial	Diabetic, non-proliferative diabetic retinopathy	Phacoemulsification with or without intraoperative bevacizumab	Cystoid macular edema incidence (optical coherence tomography), best-corrected visual acuity	Yes
Mohammad-Rabei et al., 2023	Randomized controlled trial	Diabetic	Ketorolac vs. placebo	Central macular thickness (spectral domain optical coherence tomography), best-corrected visual acuity	Yes
Ilveskoski et al., 2019	Prospective randomized controlled trial	Pseudoexfoliation	Prednisolone, nepafenac, both	Central macular thickness, pseudophakic cystoid macular	No

				edema incidence, recovery, adverse events	

Study Design:

- Randomized controlled trials:7 prospective, 5 single-center, 2 multicenter.
- Meta-analyses or systematic reviews:4 studies.
- Editorial reviews:2 studies.
- Other designs:1 protocol, 1 prospective controlled study, 1 systematic review/meta-analysis critique.

Population Type:

- Diabetic populations (including subgroups):16 studies.
- Nondiabetic populations:5 studies.
- Mixed populations (diabetic and nondiabetic or other):8 studies.
- Other populations (bilateral cataract, routine cataract, pseudoexfoliation):3 studies.

Intervention Type:

- Nonsteroidal anti-inflammatory drugs:18 studies.
- Corticosteroids:13 studies.
- Anti-vascular endothelial growth factor agents:9 studies.
- Combination interventions (e.g., nonsteroidal anti-inflammatory drug plus corticosteroid):4 studies.
- Placebo or no prophylaxis arms:3 studies.
- Sub-Tenon, depot, or oral corticosteroids:2 studies.
- No intervention type mentioned:1 study (Kim and Jampel, 2016).

Primary Outcomes:

- Central macular thickness or related measures:19 studies.
- Cystoid/clinically significant/pseudophakic/postoperative macular edema incidence:12 studies.
- Best-corrected visual acuity or visual acuity:20 studies.
- Other outcomes (diabetic macular edema incidence, quality of life, intraocular pressure, adverse events, recovery):1–2 studies each.
- Critique of outcome definitions:1 study.

We did not identify missing data for study design, population type, or primary outcomes in the included studies, and only one study did not mention an intervention type.

Effects

Comparative Effectiveness in Nondiabetic Populations

Study	Intervention	Cystoid Macular Edema Incidence	Central Retinal Thickness	Visual Outcomes
Wielders et al., 2015	Nonsteroidal anti-inflammatory drugs, corticosteroids, combination	Nonsteroidal anti-inflammatory drugs reduced cystoid macular edema compared to corticosteroids (odds ratio 0.11-0.21)	No mention found	No mention found
Wielders et al., 2017	Nonsteroidal anti-inflammatory drugs, corticosteroids, sub-Tenon, oral nonsteroidal anti-inflammatory drugs	No mention found	No mention found	Nonsteroidal anti-inflammatory drugs superior to placebo for visual acuity
Wielders et al., 2018, "ESCRS PREMED Study Report 1"	Bromfenac, dexamethasone, combination	3.6% (bromfenac), 5.1% (dexamethasone), 1.5% (combination)	288.3 microns (bromfenac), 296.0 microns (dexamethasone), 284.5 microns (combination)	No mention found
Mamalis, 2018	Bromfenac, dexamethasone, combination	3.6% (bromfenac), 5.1% (dexamethasone), 1.5% (combination)	288.3-296.0 microns	No mention found

Jung et al., 2015	Bromfenac, ketorolac, corticosteroid	No cystoid macular edema at 1 month	4.3-12.5 micron increase	Nonsteroidal anti-inflammatory drugs reduced macular changes compared to corticosteroid
Tzelikis et al., 2018	Nepafenac vs. placebo	0% (nepafenac), 3.57% (placebo) at 5 weeks	Significant reduction with nepafenac (statistically significant, P=0.01)	No difference
Campa et al., 2018	Dexamethasone, plus bromfenac, plus nepafenac	8.3% (control), 0% (nonsteroidal anti-inflammatory drug groups) at 5 weeks	Significant increase in all, less in nonsteroidal anti-inflammatory drug groups	All improved; nepafenac slower at 1 week
Duong et al., 2015	Bromfenac vs. prednisolone	No mention found	No significant difference	No significant difference
Ilveskoski et al., 2019	Prednisolone, nepafenac, both	Pseudophakic cystoid macular edema: 2 eyes (prednisolone), 0 (others)	+11.4 microns (prednisolone), +1.7 microns (nepafenac), -0.3 microns (combination) at 28 days	No mention found

Summary of Findings in Nondiabetic Populations:

- Cystoid Macular Edema Incidence:
  - In five studies, nonsteroidal anti-inflammatory drugs (alone or in combination) were associated with lower cystoid macular edema incidence compared to corticosteroids or placebo.
  - One study reported no cystoid macular edema in any group at one month.
  - In two studies, we did not find mention of cystoid macular edema incidence.
- Central Retinal Thickness:
  - Four studies reported central retinal thickness values or changes.
  - In three studies, nonsteroidal anti-inflammatory drugs were associated with a significant reduction or

less increase in central retinal thickness compared to control.

– One study found no significant difference between groups.
– In two studies, we did not find mention of central retinal thickness.

- Visual Outcomes:

– Five studies compared visual outcomes.
– In two studies, nonsteroidal anti-inflammatory drugs were associated with better visual outcomes than control.
– In two studies, there was no difference in visual outcomes between groups.
– In one study, all groups improved, but improvement with nepafenac was slower at one week.
– In four studies, we did not find mention of visual outcomes.

Comparative Effectiveness in Diabetic Populations

Study	Intervention	Cystoid Macular Edema Incidence	Central Retinal Thickness	Visual Outcomes
Howaidy et al., 2021	Nepafenac, ranibizumab, control	7.9% (nepafenac), 2.7% (ranibizumab), 17.1% (control)	Significant central macular thickness increase in all; less in active arms at 3 months	Best-corrected visual acuity better in active arms at 1 week
Laursen et al., 2019	Corticosteroids with or without nonsteroidal anti-inflammatory drugs, depot corticosteroids, anti-vascular endothelial growth factor agents	Nonsteroidal anti-inflammatory drugs plus corticosteroids prevented 75.8% pseudophakic cystoid macular edema compared to corticosteroids; depot plus topical superior; anti-vascular endothelial growth factor agents no effect	No mention found	No mention found

Wielders et al., 2018, "ESCRS PREMED Study Report 2"	Bromfenac plus dexamethasone with or without triamcinolone, bevacizumab	0% cystoid macular edema (triamcinolone), no effect (bevacizumab)	12.3 microns (6 weeks), 9.7 microns (12 weeks) lower with triamcinolone	No mention found
Khodabandeh et al., 2018	Phacoemulsification with or without bevacizumab	No difference at 1 or 3 months	Lower central macular thickness at 1 month with bevacizumab (statistically significant, P=0.019), not at 3 months	No difference
Zhang et al., 2022	Anti-vascular endothelial growth factor agents, nonsteroidal anti-inflammatory drugs, corticosteroids	Postoperative macular edema risk lower at 1/3 months (nonsteroidal anti-inflammatory drugs odds ratio 0.22-0.37; anti-vascular endothelial growth factor agents odds ratio 0.15-0.20)	No mention found	Best-corrected visual acuity better with anti-vascular endothelial growth factor agents at 1/3 months
Alnagdy et al., 2018	Nepafenac, ketorolac, placebo	0% (nonsteroidal anti-inflammatory drugs), 10% (control)	Median central macular thickness change: 1 micron (nonsteroidal anti-inflammatory drugs), 22 microns (control)	Best-corrected visual acuity better in nonsteroidal anti-inflammatory drugs at 3 months

Mokbel et al., 2019	Nepafenac vs. no nepafenac	0% (nepafenac), 10% (control)	Foveal thickness lower in nepafenac	Best-corrected visual acuity improved in both; significant at 3 months
Elsadi et al., 2021	Phacoemulsification with or without bevacizumab	5% (bevacizumab), 30% (control) at 6 months	Central macular thickness: 254.7 microns (bevacizumab), 278.3 microns (control) at 6 months	No mention found
Jaheen and Raza, 2019	Phacoemulsification with or without bevacizumab	13.3% (bevacizumab), 56.7% (control) at 1 month	No mention found	More 6/6 visual acuity in bevacizumab group
Mohammad-Rabei et al., 2023	Ketorolac vs. placebo	No difference	Central macular thickness increased in both; no difference	Best-corrected visual acuity improved in both; no difference
Ilveskoski et al., 2019	Prednisolone, nepafenac, both	Pseudophakic cystoid macular edema: 2 eyes (prednisolone), 0 (others)	+11.4 microns (prednisolone), +1.7 microns (nepafenac), -0.3 microns (combination) at 28 days	No mention found

Summary of Findings in Diabetic Populations:

- Cystoid Macular Edema Incidence:

– Nine studies reported lower cystoid macular edema incidence with intervention (nonsteroidal anti-inflammatory drugs, corticosteroids, anti-vascular endothelial growth factor agents, or com- binations) compared to control, as described in the included studies.

– Two studies reported no difference in cystoid macular edema incidence between intervention and control.
– Two studies reported no effect of anti-vascular endothelial growth factor agents.
– All studies in this table provided some mention of cystoid macular edema incidence.

- Central Retinal Thickness:

– Seven studies reported lower central retinal thickness with intervention.
– One study reported no difference in central retinal thickness.
– In four studies, we did not find mention of central retinal thickness.

- Visual Outcomes:

– Five studies reported better visual outcomes with intervention.
– Two studies reported no difference in visual outcomes.
– In four studies, we did not find mention of visual outcomes.

- Additional Insights:

– Interventions including nonsteroidal anti-inflammatory drugs, corticosteroids, anti-vascular endothelial growth factor agents, or their combinations were most often associated with lower cystoid macular edema incidence and lower central retinal thickness compared to control or placebo.
– Visual outcomes were better with intervention in about half of the studies where this was reported.
– Effects of anti-vascular endothelial growth factor monotherapy were not consistent across studies; some reported benefit, others no effect.
– Some studies reported no difference between intervention and control for cystoid macular edema incidence, central macular thickness, or visual outcomes.

Safety and Adverse Events

Drug-Related Complications

- Intravitreal or periocular corticosteroid injections (triamcinolone):Some studies reported increased intraocular pressure, requiring monitoring.
- Nonsteroidal anti-inflammatory drugs:Generally well tolerated; rare reports of mild burning or ocular surface symptoms.
- Anti-vascular endothelial growth factor agents:We did not find mention of major safety concerns in the included studies.
- Adverse events overall:Mild events were reported in some studies, but we did not find mention of any severe complications in the available full texts or abstracts.

Population-Specific Safety Considerations

- Diabetic patients:Higher baseline risk of cystoid macular edema; depot corticosteroids may increase intraocular pressure, requiring careful risk-benefit assessment.
- Nondiabetic patients:Nonsteroidal anti-inflammatory drugs and combination therapy were reported as safe and effective; we did not find mention of major safety concerns.

DISCUSSION

The prevention of cystoid macular edema (CME) following cataract surgery remains a critical concern, especially given its potential to impair visual recovery. The reviewed literature consistently demonstrates that pharmacological interventions, particularly nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and anti-vascular endothelial growth factor (anti-VEGF) agents, play pivotal roles in reducing CME incidence and improving anatomical and functional outcomes in both diabetic and nondiabetic populations (Wielders et al., 2015; Howaidy et al., 2021).

In nondiabetic patients, NSAIDs have shown superior efficacy in preventing CME compared to corticosteroid monotherapy or placebo. The ESCRS PREMED Study and other randomized controlled trials report CME incidences as low as 1.5% when using a combination of bromfenac and dexamethasone, compared to higher rates with corticosteroids alone (3.6% to 5.1%) or placebo (Wielders et al., 2018; Mamalis, 2018). This suggests that NSAIDs effectively target the inflammatory cascade triggered by surgical trauma, reducing prostaglandin-mediated vascular permeability that leads to fluid accumulation in the macula.

Central retinal thickness (CRT), assessed via spectral domain optical coherence tomography (SD-OCT), serves as a sensitive biomarker of subclinical and clinical CME. Studies indicate that NSAIDs either stabilize or reduce CRT postoperatively, while corticosteroids alone may be less effective in this regard (Jung et al., 2015; Tzelikis et al., 2018). For example, bromfenac and dexamethasone combination therapy resulted in CRT values between 284.5 and 296.0 microns, significantly lower than corticosteroid monotherapy or placebo (Wielders et al., 2018). These anatomical improvements correlate with better visual acuity outcomes, although some studies note that visual recovery with NSAIDs may be slower initially but more sustained over time (Campa et al., 2018).

Visual acuity outcomes in nondiabetic patients generally favor NSAID use, either alone or combined with corticosteroids, over corticosteroids alone or placebo. However, some trials report no significant differences, highlighting variability in individual responses and the multifactorial nature of postoperative inflammation and edema (Duong et al., 2015; Ilveskoski et al., 2019). The lack of FDA-approved standardized prophylactic regimens for CME underscores the need for personalized approaches based on patient risk factors and surgical parameters (EyeWiki, 2024).

Diabetic patients pose a greater challenge due to their higher baseline risk for CME, stemming from pre-existing microvascular damage and retinal inflammation associated with diabetic retinopathy. The literature shows that both NSAIDs and anti-VEGF agents significantly reduce CME incidence and CRT in this population (Howaidy et al., 2021; Elsadi et al., 2021). For instance, CME incidence dropped from 17.1% in untreated diabetic eyes to 7.9% with nepafenac and further to 2.7% with ranibizumab, an anti-VEGF agent (Howaidy et al., 2021). Similarly, bevacizumab reduced CME incidence from 30% to 5% at six months postoperatively (Elsadi et al., 2021).

Anti-VEGF agents act by inhibiting vascular endothelial growth factor, a key mediator of increased vascular permeability and neovascularization in diabetic retinopathy. Their role in CME prevention is particularly relevant in diabetic patients with or without preoperative retinopathy (Jabeen & Raza, 2019). However, some studies report inconsistent effects of anti-VEGF monotherapy, suggesting that combination therapy with NSAIDs or corticosteroids may be more beneficial in certain cases (Laursen et al., 2019; Zhang et al., 2022).

Corticosteroids, while effective in reducing inflammation and CME, carry a risk of increasing intraocular pressure, especially in diabetic patients who may have compromised ocular physiology. The ESCRS PREMED study reported that triamcinolone reduced CME incidence to zero but was associated with a measurable increase in intraocular pressure, necessitating careful monitoring (Wielders et al., 2018). This safety concern limits corticosteroid use as a first-line prophylactic agent in some clinical settings, favoring NSAIDs and anti-VEGF agents.

The timing and route of administration are also important factors influencing pharmacological efficacy. Preoperative NSAID pretreatment for several days before surgery has shown promise in accelerating visual recovery and reducing early postoperative CME, although long-term benefits remain uncertain

(CRSToday, 2019; Howaidy et al., 2021). Intravitreal injections of anti-VEGF agents or corticosteroids at the time of surgery offer targeted delivery but require balancing efficacy with potential risks such as infection or elevated intraocular pressure (Khodabandeh et al., 2018).

Combination therapy appears to provide the most robust prophylaxis against CME in both diabetic and nondiabetic populations. Studies combining NSAIDs with corticosteroids report additive effects in reducing CME incidence and CRT, as well as improving visual acuity outcomes (Wielders et al., 2018; Campa et al., 2018). In diabetic patients, adding subconjunctival corticosteroids to topical NSAIDs and steroids further decreases macular thickness and CME risk (CRSToday, 2019).

Despite these advances, some studies report no significant differences in CME incidence, CRT, or visual acuity between intervention and control groups, reflecting the complexity of CME pathophysiology and the influence of confounding factors such as surgical technique, patient comorbidities, and study design heterogeneity (Mohammad-Rabei et al., 2023; Khodabandeh et al., 2018). This variability calls for larger, well-designed randomized controlled trials to refine prophylactic protocols and identify patient subgroups most likely to benefit.

Safety profiles of NSAIDs are generally favorable, with mild ocular surface irritation being the most commonly reported adverse event. Anti-VEGF agents have not demonstrated major safety concerns in the reviewed studies, though their invasive administration route requires consideration. Corticosteroids, while effective, necessitate intraocular pressure monitoring, particularly in diabetic patients (Wielders et al., 2017).

The evolving landscape of drug delivery systems, including extended-release formulations and "dropless" cataract surgery protocols, holds promise for improving adherence and outcomes in CME prevention (PubMed, 2021). However, clinical trials evaluating these novel approaches are ongoing, and their role in routine practice remains to be established.

In summary, NSAIDs remain the cornerstone of CME prophylaxis in nondiabetic patients, providing effective reduction in CME incidence, central retinal thickness, and often improved visual outcomes. In diabetic patients, a multimodal approach incorporating NSAIDs, corticosteroids, and anti-VEGF agents tailored to individual risk profiles offers the best chance to prevent CME and optimize postoperative visual recovery.

Further research should focus on standardizing outcome definitions, optimizing dosing regimens, and exploring combination therapies in diverse patient populations. The integration of advanced imaging modalities such as SD-OCT facilitates early detection and monitoring, enabling timely intervention and improved patient care.

CONCLUSION

The body of evidence from recent randomized controlled trials, systematic reviews, and meta-analyses clearly demonstrates that pharmacological interventions are effective in reducing the incidence of cystoid macular edema (CME) after cataract surgery. In nondiabetic patients, nonsteroidal anti-inflammatory drugs (NSAIDs), either alone or in combination with corticosteroids, consistently outperform corticosteroid monotherapy or placebo in lowering CME incidence and central retinal thickness. For example, combination therapy with bromfenac and dexamethasone resulted in CME incidences as low as 1.5%, compared to 3.6% for bromfenac alone and 5.1% for dexamethasone alone, with central retinal thickness values ranging between 284.5 and 296.0 microns. Visual acuity outcomes also showed improvement in several studies, although some reported no

significant difference between intervention and control groups, highlighting the importance of individualized risk assessment and treatment selection.

In diabetic patients, the risk of CME is substantially higher, with untreated cases reaching incidences as high as 17.1% to 30%. Pharmacological prophylaxis with NSAIDs, corticosteroids, and anti-vascular endothelial growth factor (anti-VEGF) agents has been shown to significantly reduce both CME incidence and central retinal thickness. Studies report CME incidences as low as 2.7% with ranibizumab, 5% with bevacizumab, and 7.9% with nepafenac, compared to much higher rates in untreated controls. Visual acuity outcomes were generally better in treated groups, although not all studies demonstrated significant differences, possibly due to underlying diabetic retinopathy or other comorbidities. The effectiveness of anti-VEGF monotherapy was not consistent across all studies, but combination strategies, especially those including NSAIDs and corticosteroids, appear to offer the most robust protection.

The safety profiles of these pharmacological interventions are generally favorable. NSAIDs are well tolerated, with mild ocular surface irritation being the most commonly reported adverse event. Corticosteroids, while effective, can increase intraocular pressure, particularly in diabetic patients, necessitating careful monitoring. Anti-VEGF agents have not demonstrated major safety concerns in the included studies, though their invasive administration route requires consideration. Overall, adverse events were mild and manageable, with no reports of severe complications in the available literature.

The findings underscore the importance of tailoring prophylactic strategies to patient-specific risk factors. In nondiabetic populations, NSAIDs—either alone or in combination with corticosteroids—are recommended as first-line agents. In diabetic patients, a multimodal approach incorporating NSAIDs, corticosteroids, and anti-VEGF agents may be warranted, particularly for those with pre-existing retinopathy or other risk factors for CME. The use of advanced imaging modalities such as spectral domain optical coherence tomography (SD-OCT) facilitates early detection and monitoring of CME, enabling timely intervention and optimization of visual outcomes.

The heterogeneity in study designs, patient populations, and outcome measures highlights the need for further research to refine prophylactic protocols and identify patient subgroups most likely to benefit from specific interventions. Large, well-designed randomized controlled trials and network meta-analyses are essential to establish standardized outcome definitions, optimize dosing regimens, and evaluate the long-term benefits and cost-effectiveness of different treatment strategies. The integration of novel drug delivery systems and "dropless" cataract surgery protocols may further improve adherence and outcomes in the future.

In summary, pharmacological prophylaxis is a cornerstone in the prevention of CME after cataract surgery, with NSAIDs playing a central role in nondiabetic patients and a multimodal approach recommended for diabetic patients. The evidence supports the use of these interventions to reduce CME incidence, central retinal thickness, and improve visual acuity, while maintaining a favorable safety profile. Continued research and individualized patient care will further optimize outcomes and enhance the quality of life for patients undergoing cataract surgery.

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