

SYSTEMATIC REVIEW · CLINICAL PERSPECTIVE

# Breaking the Vicious Cycle

## Glaucoma Medication — OSD — Reduced Efficacy A Role for JETT Bioelectric Modulation

Ocular Surface Damage & Drug Utilization of  
Glaucoma Eye Drops

A Systematic Review with Literature References

Glaucoma · OSD · BAK · Goblet Cells · Adherence

PF · FDC · SLT/MIGS · **JETT Neuro-Bioelectric Modulation**

THE BURDEN · MEDICATION-INDUCED OSD



A NEW PATH · JETT MEDICAL II



JETT Medical II system · console, handpiece & applicators

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# The Clinical Paradox of Glaucoma Eye Drops

When the Treatment Becomes Part of the Problem

GLOBAL BURDEN • 2020

76M

patients worldwide; 3.61M blind (8.39% of global blindness). Projected >110M by 2040.

CHINA • AGE 40+

21.8M

patients (prevalence 3.12%). Awareness rate only 16.8%; treatment rate even lower.

STANDARD TREATMENT

IOP-lowering

eye drops — the only proven therapy to slow progression. Initial & long-term choice for most patients.

The Vicious Cycle: Medication → Ocular Surface Damage → Reduced Efficacy

Preservatives (especially benzalkonium chloride, BAK) and active ingredients in eye drops chronically damage the ocular surface. This damage triggers reflex tearing, inflammation, and non-adherence — all of which reduce drug bioavailability. When IOP remains uncontrolled, clinicians typically add another medication, which further worsens the ocular surface. Many patients on 2–4 drops remain uncontrolled because the real issue is not insufficient drug, but **pseudo-resistance from ocular surface disease and poor adherence**.

# Global Glaucoma Prescription Patterns

PGA Dominance, Polypharmacy, and BAK Prevalence

## Regional Comparison of Glaucoma Medication Characteristics

| Region        | First-line          | Polypharmacy | PF Adoption  | Key Features                                               |
|---------------|---------------------|--------------|--------------|------------------------------------------------------------|
| North America | PGA                 | 40–50%       | Low          | Brand drugs dominate; SLT as first-line gaining acceptance |
| Europe        | PGA                 | 50–55%       | High         | PF recommended in guidelines; FDC widely used              |
| Asia-Pacific  | PGA, β-blocker      | 55–65%       | Low–Moderate | Japan: high FDC use; China: generics rising                |
| China         | PGA, β-blocker, CAI | 50–60%       | Very Low     | BAK multi-dose bottles dominate; low treatment rate        |
| Latin America | PGA                 | 54.7%        | Low          | 94.1% use preserved drops; public/private gap              |

BAK DOMINANCE

~70% of ophthalmic preparations contain BAK. 94.1% of Colombian patients used preserved antiglaucoma drugs; 68.4% contained BAK [7].

OVER-PRESCRIPTION

Japanese study: monthly prescribed drops were **2.4× the theoretical need** (avg +1.4 bottles), indicating a huge gap between prescription and actual use [27].

Sources: [7,13,16,23,27] · Table 1 from the review

# PGA, Polypharmacy & Fixed-Dose Combinations

First-line Therapy, Combination Burden, and the FDC Advantage

## PGA — GLOBAL FIRST-LINE

**Agents:** latanoprost, travoprost, bimatoprost, tafluprost

**Efficacy:** IOP reduction 25–35% (~6–9 mmHg) as monotherapy

**Advantage:** once-daily dosing, favorable systemic profile

**Market:** Asia-Pacific 42.3%, N. America 26–38%, Europe 26–31%

## POLYPHARMACY — THE REALITY

- Colombia (n=38,259): **54.7%** on combination therapy; 41.3% use FDC [7]
- N. India: avg 1.41–1.51 bottles; **62.5%** use ≥2 drugs [23]
- Japan (n=5,303): high multi-drug rate in outpatient clinics
- Each additional BAK-preserved drop linearly increases daily exposure

## FIXED-DOSE COMBINATIONS

### Fewer Drops → Better Adherence → Healthier Ocular Surface

**Adherence:** PDC 79.1% (FDC) vs 62.2% (free combo),  $P < 0.0001$  [16]

**LTFC study:** switching to latanoprost/timolol FDC improved adherence at 3 & 6 months ( $P = 0.001$ ) and OSD signs ( $P < 0.01$ ) [26]

**PF-TTFC:** preservative-free tafluprost/timolol reduced 24h IOP from 17.8→15.3 mmHg ( $P < 0.001$ ) [21]

## COMMON FDC FORMULATIONS

- PGA / timolol (latanoprost, travoprost, bimatoprost, tafluprost)
- Dorzolamide / timolol · Brinzolamide / timolol
- Brimonidine / timolol · Brinzolamide / brimonidine

# OSD Epidemiology in Glaucoma Patients

Prevalence Far Exceeds the General Population — A Dose-Response Relationship

## OVERALL PREVALENCE

**48–75%**

of glaucoma patients have OSD symptoms, vs. ~10–20% in general population. 22–78% have clinical signs [9].

## MULTICENTER STUDY (n=448)

**59.2%**

Mild: 25.7% • Moderate: 13.2%

**Severe: 20.3%**

One in five patients has severe OSD [3].

## JAPAN POAG STUDY

**62.7%** subjective dry eye symptoms

**73.1%** reduced tear secretion (Schirmer  $\leq 10$ mm)

**56.7%** TBUT  $\leq 5$  seconds [8]

## Key Evidence: Dose-Response Relationship Suggests Causation

- Croatia: dry eye symptoms in **75%** of glaucoma users vs. **30%** of healthy controls [5]
- India: OSD prevalence **60.7%** in glaucoma vs. **19.7%** in non-glaucoma ( $P < 0.01$ ) [3]
- Large registry (n=19,665): **52.6%** of glaucoma patients had concurrent DED diagnosis [17]
- OSD severity correlates positively with **number of medications and duration of use** — patients on multiple BAK-preserved drops show worse conjunctival inflammation, squamous metaplasia, and goblet cell loss [2,5]

# BAK Toxicity: Multi-Structure Damage Pathways

Benzalkonium Chloride — A Cationic Detergent That Damages Far Beyond the Ocular Surface

BAK is a cationic surfactant (positively charged head + hydrophobic C8–C16 alkyl chain) that strongly interacts with negatively charged phospholipids, disrupting cell membranes — its "detergent" property kills microbes but also damages ocular tissues in a dose-dependent manner.

| Target Structure    | Toxicity Mechanism                                                               | Clinical Consequence                                                               |
|---------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Tear Film           | Disrupts lipid layer, reduces TBUT, alters osmolarity                            | Unstable tear film, evaporative dry eye                                            |
| Conjunctiva         | Apoptosis at very low concentrations, squamous metaplasia, IL-6/IL-8 release     | Conjunctival hyperemia, inflammation, reduced mucin                                |
| Goblet Cells        | Destabilization, density reduction                                               | Mucin layer deficiency, tear film breakup                                          |
| Corneal Epithelium  | Tight junction disruption (occludin, ZO-1), MMP-9 upregulation, barrier loss     | Positive staining, epithelial defects, delayed healing                             |
| Corneal Nerves      | Reduced nerve fiber density, diminished neurotrophic support                     | Reduced tearing, sensory abnormalities; "nerve damage → dry eye" positive feedback |
| Trabecular Meshwork | BAK reaches TM (mass spectrometry confirmed); apoptosis, oxidative stress, MMP-9 | Paradoxical IOP elevation, reduced aqueous outflow                                 |
| Tenon's Capsule     | Fibroblast activation, scarring tendency, MMP-9 expression                       | Increased risk of filtration surgery failure                                       |

Sources: [2,5,11] · Table 2 from the review · Dose-dependent: 0.0025% microvilli loss → 0.005% cell shrinkage → 0.01% epithelial exfoliation

# Active Drug Effects & Cumulative Damage

Not Just Preservatives — Active Ingredients Contribute Independently; Polypharmacy Synergizes Damage

## β-BLOCKERS

Timolol, betaxolol, carteolol  
After correcting for BAK exposure, still significantly reduce TBUT and increase corneal staining [3].  
Reduce tear secretion and destabilize pre-corneal tear film.

## PGA

Even PF 0.005% latanoprost reduces tearing, causes goblet cell loss, epithelial barrier disruption [5].  
Unique: conjunctival hyperemia, periorbital fat atrophy, iris pigmentation [3].

## CAI

Dorzolamide, brinzolamide  
Generally well-tolerated, but rabbit study: dorzolamide with lowest BAK (0.0075%) caused more OSD than higher-BAK latanoprost/timolol [3].

## α2-AGONISTS

Brimonidine  
Allergic conjunctivitis in 10–15%, follicular conjunctivitis, eyelid contact dermatitis — often leads to discontinuation [5].

## Cumulative Effect of Polypharmacy: Synergistic, Not Additive

- Each additional BAK-preserved drop **linearly increases daily BAK exposure**; tear film clearance capacity is finite
- With 3–4 medications (6–8 daily instillations), the ocular surface is **almost continuously exposed** to preservatives with virtually no recovery window
- Drug-drug washout: a subsequent drop flushes the preceding one before absorption — **reducing efficacy while increasing total exposure** [1]
- Guidelines recommend ≥5 min interval between drops, but real-world adherence rarely meets this requirement

# Ocular Drug Absorption & Bioavailability

Only 1–5% of an Eye Drop Reaches the Anterior Chamber

1

## Tear Dilution & Clearance

Tear vol 7–10 µL vs. drop 25–50 µL; >90% lost in minutes via nasolacrimal drainage

2

## Corneal Epithelial Barrier

5–7 cell layers, tight junctions (pore ~2.0 nm); lipophilic epi + hydrophilic stroma = dual filter

3

## Conjunctival-Scleral & Systemic Loss

Large surface but rich vasculature = rapid systemic clearance; efflux pumps & CYP450 metabolism

### NET RESULT — CORNEAL BIOAVAILABILITY

1–5%

of the prescribed dose reaches the anterior chamber. The vast majority is wasted — this inherent inefficiency is the baseline upon which OSD further reduces drug utilization.

## Key Pharmacokinetic Parameters

**Tear volume:** 7–10 µL

**Drop volume:** 25–50 µL

**Tear turnover:** 16%/min

**Conjunctival t<sub>1/2</sub>:** 1–2 minutes

**Paracellular pore:** ~2.0 nm

**MW cutoff:** <5,000 Da

**Bioavailability:** 1–5%

# How OSD Impairs Drug Utilization

Multiple Mechanisms — From Reflex Tearing to Inflammatory Interference with Drug Targets

| Mechanism                      | Direction                      | Evidence Strength | Key Reference                                 |
|--------------------------------|--------------------------------|-------------------|-----------------------------------------------|
| Reflex tearing dilutes drug    | ↓ Bioavailability              | Moderate          | Wang 2025 [29] — physiology well-established  |
| Corneal barrier disruption     | Theoretical ↑, actual unstable | Low-Moderate      | BAK as penetration enhancer [2]               |
| BAK reaches TM → apoptosis     | ↓ Aqueous outflow              | Moderate          | Garcia-Feijoo 2021 [11] — mass spec confirmed |
| Subconjunctival fibrosis       | ↓ PGA efficacy                 | Low-Moderate      | Ruiz-Lozano 2023 [5] — mechanistic            |
| MMP-9 / inflammatory mediators | Barrier & ECM disruption       | Moderate          | Zaleska-Żmijewska 2019 [19]                   |
| Adherence collapse             | Actual dose << prescribed      | High              | Schwartz 2008 [1]; Singh 2024 [25]            |

**Most underappreciated mechanism:** inflammatory mediators (IL-6, IL-8, MMP-9, TNF-α) diffuse beyond the ocular surface, interfering with drug targets in the trabecular meshwork and ciliary body — the drug's substrate is already damaged.

# Clinical Evidence & Adherence Collapse

Treating OSD Improves IOP Control — While Non-Adherence Undermines Everything

## Clinical Evidence: Treat OSD → IOP Improves

Dubrulle et al. 2018 — 10 cases

After aggressive OSD treatment (PF drops, artificial tears, anti-inflammatory), mean IOP fell **23.75 → 15.15 mmHg (−36.2%, P=0.007)**, even with fewer medications [6].

PF-TTFC 24h IOP study

Switching from BAK-latanoprost to PF tafluprost/timolol FDC: 24h IOP **17.8 → 15.3 mmHg (P<0.001)**, evening −18.5% [21].

FREE study — 12 months, PF latanoprost

IOP remained stable while conjunctival hyperemia and OSD signs **significantly improved (P<0.05)** [22].

**Reverse proof:** "Uncontrolled IOP" was often pseudo-resistance from OSD and poor utilization — treating the surface restores true drug efficacy.

## Adherence Collapse — The Real "Efficacy Killer"

NON-ADHERENCE RATE

**30–80%** across published studies, worsening over time [1].

**GAPS study:** ~95% of patients claim "perfect adherence," but objective data tells otherwise. Even under electronic monitoring, **45% of doses** were incorrect [1].

**Causes:** forgetting (71%), cost (26%), polypharmacy (21%), side effects — primarily OSD discomfort [25].

**The illusion:** "on 4 medications" often means only 1–2 are used regularly; the rest occasionally irritate the surface [18].

# Solutions I: PF Formulations & New Preservatives

Eliminating or Reducing BAK — The Most Direct Intervention

## PRESERVATIVE-FREE (PF) FORMULATIONS

### Delivery formats

- Unit-dose vials · Multi-dose anti-contamination systems (COMOD, ABAK)

### Clinical evidence

- IOP efficacy equivalent to BAK (difference <1 mmHg, clinically insignificant)
- OSD signs/symptoms significantly improved: less hyperemia, less corneal staining, longer TBUT, lower OSDI [4,9,22]
- PF bimatoprost gel Phase III: IOP ↓ 31–35% vs 32–36%; fewer adverse events [12]
- PF latanoprost cationic emulsion (CE): 15-month open-label — sustained IOP control + continuous OSD improvement, no serious AEs [24]

### Global adoption

- Europe leads (guidelines recommend PF for OSD/polypharmacy)
- US lags (limited options, higher cost); Asia-Pacific & China: very low penetration [4,7]

## NOVEL LOW-TOXICITY PRESERVATIVES

### Polyquad (polyquaternium-1)

- Large molecule (~16,000 Da), poorly penetrates corneal epithelium
- Inactivated by binding to negatively charged mucins in tears
- Travoprost Polyquad vs BAK: lighter OSD, equivalent IOP reduction (7.2 vs 6.0 mmHg) [10]

### SofZia

- Zinc-ion buffered system (zinc + sorbitol/mannitol/propylene glycol)
- Neutralized by natural tear buffering; low toxicity

### Purite (stabilized oxychloro complex)

- Reduced in tears to natural tear components (Na, Cl, water)
- Low irritation

**Common advantage:** multi-dose bottle convenience with significantly reduced ocular surface toxicity — important complement to PF [2,10].

# Solutions II: FDC & Sustained Release Systems

Fewer Drops, Less Preservative, or No Drops at All

**Fixed-Dose Combinations (FDC):** reduce drop frequency and total preservative exposure. Adherence PDC 79.1% vs 62.2% (free combo). PF-TTFC switching: OSD improves + IOP lowers and stabilizes, even from "maximally tolerated therapy" [16,21,26].

## Sustained Release Drug Delivery Systems

| Product                  | Drug              | Route                             | Duration            | Status               | Key Advantages / Concerns                                                                |
|--------------------------|-------------------|-----------------------------------|---------------------|----------------------|------------------------------------------------------------------------------------------|
| Durysta                  | Bimatoprost 10 µg | Intracameral (biodegradable PLGA) | 4–6 mo (25% → 2 yr) | FDA 2020             | First approved sustained-release; concerns: IOP spike, endothelial loss, single-use only |
| iDose TR                 | Travoprost 75 µg  | Intracameral (non-degradable Ti)  | 36 months           | FDA approved         | Long-acting, replaceable; concerns: requires removal/exchange, endothelial monitoring    |
| OTX-TP                   | Travoprost        | Punctal plug (PEG hydrogel)       | 90 days             | Clinical             | Non-invasive, reversible; concerns: retention rate, foreign body sensation               |
| Nano-emulsion / Liposome | Various           | Topical drop                      | 12–24 h             | Pre-clinical / Early | 2–5× higher corneal concentration & AUC; concerns: long-term safety                      |
| Cationic Emulsion (CE)   | Latanoprost (PF)  | Topical drop, QD                  | Daily               | Marketed (EU)        | PF + prolonged pre-corneal retention; 15-month data favorable [24]                       |

Sources: [14,15,20,21,24,26,29] · Table 4 from the review

# Solutions III: Laser/MIGS & OSD Treatment

Reducing Medication Burden and Actively Repairing the Ocular Surface

## LASER & MINIMALLY INVASIVE SURGERY

### SLT — Selective Laser Trabeculoplasty

- IOP reduction 20–30%, non-inferior to PGA monotherapy
- LiGHT trial: as first-line, significantly reduces drop need [28]
- >50% of patients reduce  $\geq 1$  topical medication; repeatable, cost-effective
- **Zero preservative exposure, zero adherence issue**

### MIGS — iStent, Hydrus, OMNI, XEN, Trabectome

- Average medication reduction 0.79 drugs; some patients stop entirely [18]
- iStent Inject contralateral study: hyperemia 2.4→2.0 ( $P=0.003$ ), Oxford staining 1.6→0.7 ( $P<0.001$ ); control eye unchanged [30]
- Hydrus vs SLT: IOP ↓ 26% vs 31%, medication reduction 39% vs 20% at 12 mo

**Direct proof:** reducing medication directly improves the ocular surface.

## OCULAR SURFACE REPAIR & ANTI-INFLAMMATION

### Artificial tears — Sodium hyaluronate (HA)

- Scavenges BAK-induced ROS, stabilizes tear film, promotes epithelial healing
- Use PF artificial tears,  $\geq 5$ –10 min apart from IOP-lowering drops
- Severe cases: 0.3% high-concentration HA [11]

### Anti-inflammatory therapy

- Cyclosporine A (CsA): inhibits T-cell activation, improves OSD signs [9]
- Lifitegrast: blocks LFA-1/ICAM-1 interaction
- Corticosteroids (loteprednol 0.25%): short-term pulse for moderate-severe OSD; monitor IOP & cataract [5]

### Comprehensive management

- MGD treatment (warm compresses, lid hygiene, IPL), humidifiers,  $\omega$ -3 fatty acids [3,9]

# JETT Medical II: A New Therapeutic Axis

Multi-Target Neuro-Bioelectric Modulation for Medication-Induced Ocular Surface Disease

## What Is JETT?

**Device system** — console + handpiece + precision applicators for lids, fornix and lid margin

**Physical principle** — controlled, sub-threshold DC pulsed electric field (16–136 mV/mm), within the eye's endogenous healing range (42 mV/mm), far below electroporation

**Procedure** — non-invasive, office-based, serial sessions (typically 5–8 at 1–2 week intervals)

**Philosophy** — treats the lacrimal functional unit (LFU) as one integrated system, not individual parts

**Key distinction from AC/RF/IPL** — DC delivers directional charge transport that cells can navigate (galvanotaxis); AC net charge = 0

## Why JETT for Glaucoma OSD?

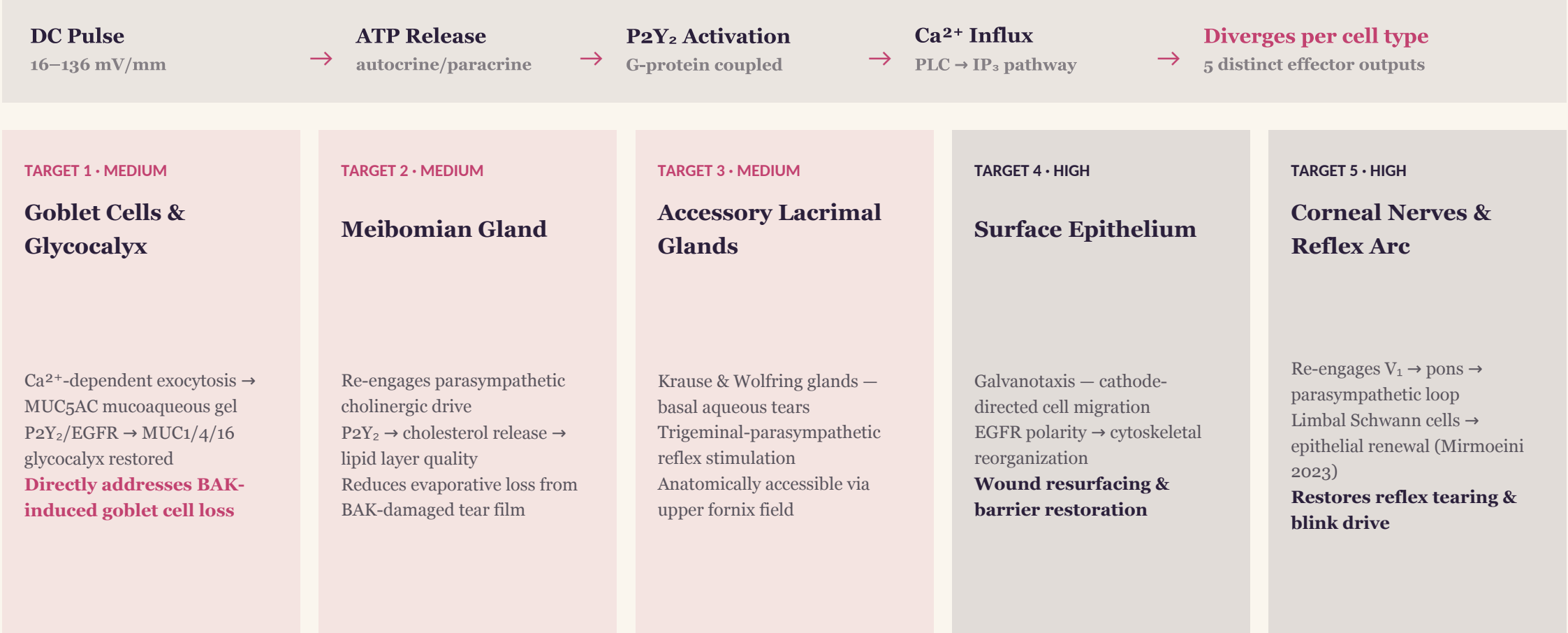
**The unmet need** — PF, FDC, SLT and MIGS reduce preservative exposure or bypass drops, but none directly repair the already-damaged conjunctival surface (goblet cell loss, MUC5AC deficiency, squamous metaplasia, chronic inflammation)

**JETT fills the gap** — targets goblet cells, mucin-glycocalyx, epithelium and neural reflex arc — the exact structures damaged by long-term glaucoma medication

**Dual potential** — repair ocular surface **and** improve drug bioavailability, potentially reducing required drug burden while stabilizing or further lowering IOP

# One Cascade, Five Cellular Targets

DC pulse → ATP → P2Y<sub>2</sub> → Ca<sup>2+</sup> — a universal upstream signal that diverges by cell type



# Targeting the Conjunctiva–Goblet Cell–Inflammation Axis

How glaucoma drops damage the surface — and how JETT repairs each layer

## WHAT GLAUCOMA MEDICATION DOES

**BAK toxicity** — goblet cell apoptosis, MUC5AC depletion, squamous metaplasia (Grade 0→3)  
**Chronic inflammation** — IL-1β/6/8, TNF-α, MMP-9 upregulation; conjunctival hyperemia  
**Epithelial barrier** — tight junction disruption (occludin, ZO-1), delayed healing  
**Neural damage** — reduced corneal nerve fiber density, blunted reflex tearing  
**Net result** — tear film instability → reflex tearing dilutes drug → reduced bioavailability → adherence collapse → IOP escalation → more drops



## HOW JETT REPAIRS EACH LAYER

**Goblet cells** — P2Y<sub>2</sub>/Ca<sup>2+</sup> → MUC5AC exocytosis from residual goblet cells; glycocalyx MUC1/4/16 restored  
**Inflammation** — galvanotactic epithelial migration → barrier restoration → breaks self-sustaining inflammatory cycle  
**Epithelial barrier** — directional cell migration → wound resurfacing, tight junction reformation  
**Neural reflex** — re-engages trigeminal-parasympathetic arc → restores reflex tearing & blink drive  
**Net result** — surface integrity restored → improved drug retention & bioavailability → potential to reduce drug burden

OSDI ↓78% Rau ESCRS 2022

TBUT ↑40% 77 pts + 22 sham

DEQ-5 ↑90% Zemanova 2020, 40 eyes

# Reducing Drug Burden While Stabilizing IOP

A proposed algorithm for glaucoma patients with medication-induced OSD

## Integrated Treatment Pathway

1

**Identify OSD** — screen all multi-drug glaucoma patients: OSDI, TBUT, corneal staining, MMP-9. OSD is present in 48–75% but rarely quantified.

2

**Optimize regimen** — switch BAK→PF, free combo→FDC, drop low-marginal-benefit drugs. Reduce preservative load before adding interventions.

3

**Add JETT course** — 5–8 sessions over 6–10 weeks to repair goblet cells, epithelium and neural reflex arc.

4

**Reassess IOP at 4–8 weeks** — improved surface integrity increases drug retention and bioavailability; many patients stabilize without added medication.

5

**Step down or intervene** — reduce medication frequency if IOP stable; if still uncontrolled on optimized regimen, consider SLT/MIGS rather than adding drops.

DUAL BENEFIT HYPOTHESIS

• **Surface repair** → improved tear film stability → less reflex tearing → better drug retention → lower effective dose needed

• **Reduced inflammation** → less conjunctival scarring → improved trabecular outflow (BAK also damages TM via MMP-9)

• **Better adherence** → fewer drops, less burning → more consistent IOP control

CALL TO ACTION FOR GLAUCOMA SPECIALISTS

Glaucoma-specific JETT evidence is currently limited — this is a research opportunity, not a limitation.

**Proposed study design:** prospective, single-arm or sham-controlled — multi-drug POAG/OAG with OSD → JETT course → primary endpoint: change in number of medications with IOP maintained ≤ target.

# Clinical Decision Framework & Conclusion

"Treat the Ocular Surface First, Then Reassess Efficacy"

## 5-Step Clinical Pathway

- 1

Assess real adherence — don't assume compliance; check bottle counts, e-monitoring; fix adherence before adding drugs
- 2

Assess OSD severity — OSDI, TBUT, corneal staining, Schirmer, MMP-9; treat moderate-severe OSD
- 3

Reduce toxicity & frequency — switch BAK→PF, free combo→FDC, drop low-marginal-benefit drugs
- 4

Reassess IOP after 4–8 weeks — many patients improve without adding medication
- 5

If still uncontrolled → SLT or MIGS, not a 4th or 5th drop

**WHEN TO STOP ADDING DROPS**

≥3 drug classes still uncontrolled · moderate-severe OSD · fluctuating IOP suggesting non-adherence · patient burnout/cost · progressing visual field

KEY CONCLUSIONS

- OSD from glaucoma drops is **underestimated but evidence-rich** (48–75% prevalence)
- BAK damages tear film, epithelium, nerves, and even trabecular meshwork
- OSD impairs drug utilization via reflex tearing, inflammation, and **adherence collapse**
- Solutions exist: PF, FDC, sustained release, SLT/MIGS, OSD treatment
- The shift: from "add drops" to "**optimize surface, reduce burden, intervene early**"

FUTURE DIRECTIONS

- **Gene therapy** — single-treatment long-term IOP control
- **Smart delivery** — stimuli-responsive nanoparticles, wearable devices, smart bottles
- **Biomarker-guided** personalized therapy (tear MMP-9, inflammatory profiles)
- **Paradigm shift** — early SLT/MIGS, less medication dependence, surface protection

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