New Drugs in Glaucoma Treatment

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With new targets and new mechanisms of action, emerging therapeutics are likely to improve outcomes and reduce the therapeutic burden of glaucoma.

Primary open-angle glaucoma (POAG) is a neurodegenerative eye disease that causes progressive and potentially blinding damage, primarily to the optic nerve. At present, intraocular pressure (IOP) is the only established, treatable risk factor and therefore the target for all available treatments for glaucoma. The standard treatment for patients with newly diagnosed POAG has traditionally been medical. More invasive therapeutic options, such as laser trabeculoplasty or surgical intervention, are typically reserved for patients for whom medical therapy has proved inadequate or impractical.

CURRENT MEDICAL OPTIONS

Current IOP-lowering medications can be divided into six categories based on their chemical properties and pharmacologic action:

- Carbonic anhydrase inhibitors (CAIs), which can be systemic or topical;
- Alpha-2 adrenergic agonists (eg, brimonidine and apraclonidine);
- Beta adrenergic antagonists, ie “beta-blockers,” such as timolol, betaxolol, and levobunolol;
- Cholinergic agonists (eg, pilocarpine and carbachol);
- Beta-2 adrenergic agonists (eg, epinephrine); and
- Prostaglandin analogs (PGAs), (eg, latanoprost, travoprost, tafluprost, and bimatoprost).

The first three classes—CAIs, alpha-2 adrenergic agonists, and beta-blockers—are secretory suppressants that decrease aqueous humor production. Carbonic anhydrase catalyzes the reaction that produces bicarbonate ions in the ciliary body. Inhibition of the enzyme hampers ion and fluid transport across the ciliary epithelium and thus reduces aqueous secretion. Beta-blockers, once the most popular choice for the medical management of glaucoma, and alpha-2 agonists act on different receptors to reduce aqueous humor formation and IOP by inhibiting the synthesis of cyclic adenosine monophosphate (cAMP) and thus its downstream effects in the ciliary epithelium. In addition to decreasing aqueous production, alpha-2 agonists may also increase uveoscleral outflow contributing to their IOP reduction.

ENHANCING OUTFLOW

Cholinergic agonists, beta-2 adrenergic agonists, and PGAs lower IOP by enhancing aqueous outflow.

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Measuring IOP: The Technology and Its Limitations
by James C. Tsai, MD, MBA
Cholinergic agonists contract the ciliary muscle, pulling the scleral spur, distorting the trabecular meshwork, and widening Schlemm’s canal to facilitate conventional aqueous outflow (Figure 1). PGAs, on the other hand, increase uveoscleral outflow by relaxing the ciliary muscle and reducing the synthesis and release of certain matrix metalloproteinases and thereby remodeling its extracellular matrix. PGAs are currently the most effective topical IOP-lowering agents and have become the most widely used first-line agents for glaucoma management in the US.

While multiple medical therapies are available for lowering IOP, the therapeutic armamentarium for glaucoma has remained essentially stagnant for nearly two decades, excepting various combinations of the above molecules in one bottle. Since the mid-to-late 1990s, when selective alpha-2 agonists, topical CAIs, and PGAs were introduced, no new class of glaucoma drug has come to the market. This lack of advancement in pharmacotherapy for glaucoma does not reflect lack of research and development. Quite the opposite: years of work have filled the glaucoma drug pipeline with a number of promising compounds and classes, several of which have reached late-stage clinical trials. For the first time in 20 years, the spectrum of pharmacologic options for treating glaucoma appears to be on the verge of significant expansion.

THE NEED FOR ADDITIONAL MEDICATIONS

The aim in medical therapy of glaucoma is to reduce the burden of treatment and inhibit optic neuropathy. At this point, the only way we know how to do this in humans is by lowering IOP. PGAs lower IOP effectively, yet most glaucoma patients require more than one medication—or medication plus a laser or surgical treatment—to bring IOP down into their particular “safe” zone. Used once a day, they produce an IOP reduction of about 30%,1,2 Since the introduction of PGAs, the number of penetrating drainage surgeries for glaucoma performed annually has reportedly dropped.4,6 That said, since monotherapy is insufficient to achieve adequate IOP lowering in a majority of patients, additional agents are desirable to provide greater IOP lowering efficacy, either by themselves or in combination with existing drugs.

In a particular patient or group of patients, one class of medication may lose its effectiveness over time, a pharmacological effect known as tachy-
phyllaxis. The PGAs are quite resistant to development of tachyphyllaxis, but adjunctive therapy for additional pressure reduction can become necessary due to progression of the disease. When a patient requires three or four medications for IOP control, the therapeutic burden—primarily the complexity of the treatment regimen rather than just its cost, since many of the glaucoma drugs are now available as generics—increases significantly.

Adequate IOP Reduction

Some glaucoma patients, including some with normal tension glaucoma, require greater IOP reduction than others. For these particular patients, effective IOP reduction may require pressures close to 10 mm Hg around the clock. With the medications we have currently, it is nearly impossible to reduce pressures to such a level. Even with multiple medications, pressures in this range are difficult to attain. Theoretically, combining agents with different mechanisms of action should generate additive IOP-lowering effect. It does, but clinical evidence suggests that the additive IOP-lowering efficacy of any agent with other classes of agents is typically not as substantial as one would hope.

A meta-analysis of ten randomized clinical trials of the IOP-lowering efficacy of alpha-2-adrenergic agonists, beta-blockers, and topical CAIs used in combination with a PGA found that mean diurnal IOP reductions with all three adjunctive therapies were similar, ranging from 2.3 to 3.0 mm Hg.7 Fixed combinations of timolol and a PGA have not been able to demonstrate substantial additional IOP-lowering effect compared to PGAs alone, and are not approved in the US.8,9 In a recent clinical study that compared the fixed combination of latanoprost and timolol with latanoprost alone, the mean IOP difference between the two treatment groups (the fixed combination therapy minus latanoprost monotherapy) ranged from −1.52 to −0.54 mm Hg.9

Drainage surgery, such as trabeculectomy or tube shunt procedures, can achieve pressures in the low teens. But not all patients are good surgery candidates, and some may still need medication after the surgery. And drainage surgery has its own considerable set of risks and challenges. At the end of the day, there is always a need for better medications, medications that work well together, and medications that can reduce IOP to near 10 mm Hg, either by themselves or in combination.

Nitric Oxide-donating Compounds

Latanoprostene bunod is a nitric oxide-donating prostaglandin F2-alpha analog currently in phase 3 clinical trials. Instead of combining two agents in one bottle, two molecular entities—latanoprost and a nitric oxide (NO) donating moiety—are in essence fused into one molecule. While latanoprost enhances uveoscleral outflow, nitric oxide by itself increases outflow facility across the trabecular meshwork. Although its mechanism of action is not fully elucidated, nitric oxide appears to work by direct action on the trabecular meshwork to increase outflow facility. Specifically, it likely works as a signaling molecule that is part of the trabecular meshwork’s natural response to deformation stemming from the pressure differential between the anterior chamber and Schlemm’s canal. In this scenario, nitric oxide signals the trabecular meshwork cells to adjust to their contractile tone so that collectively the meshwork maintains a preset deformation and intraocular pressure. NO is thought to suppress the Rho signaling pathway (see below), which when activated, contracts the trabecular meshwork to increase outflow resistance. Thus, if IOP rises, meshwork deformation is greater, endothelial nitric oxide synthase is upregulated, and more NO is released, causing the TM cells individually and the TM as a whole to relax. The effect is that outflow resistance decreases to reduce the IOP toward its preset norm.

In clinical studies, latanoprostene bunod has demonstrated substantial additivity of its two different IOP-lowering mechanisms. In the phase 2b VOYAGER study, it consistently lowered IOP in a dose-dependent manner. All four doses tested showed greater IOP reduction compared with latanoprost 0.005%, alone, with the differences for two higher doses (0.024% and 0.040%) reaching more than 1 mm Hg at the majority of time points for up to at least 28 days.10 Two phase 3 clinical trials—APOLLO and LUNAR—compared the efficacy and safety of once daily latanoprostene bunod to that of twice-daily timolol. Top-line results of both studies showed that latanoprostene bunod had a statistically superior (P < 0.05) IOP-lowering effect compared to timolol alone, with a reduction in mean IOP of 7.5 to 9.1 mm Hg from baseline between 2 and 12 weeks of treatment.11

Cytoplasmic Agents

Nitric oxide may act like a Rho kinase (ROCK) inhibitor, whereas Rhopressa and Roclatan—another two potential glaucoma drugs currently in phase 2 and 3 development—are actual ROCK inhibitors. Trabecular meshwork cells are...
highly contractile due to an abundance of actin filaments, a primary cytoskeletal component that drives cell contractility via interaction with motor proteins such as myosin. Activation of the Rho pathway tightens actomyosin networks, contracting the cells and strengthening cell-extracellular matrix adhesion. Overall, this makes the trabecular meshwork, especially the juxtacanalicular tissue, stiffer and more resistive to the outflow of aqueous humor. ROCK inhibition reduces actomyosin contractility and relaxes the meshwork, allowing aqueous to pass through more easily.

Interestingly, Rhopressa is claimed to have two additional effects. Besides ROCK, it may also inhibit norepinephrine transporters, leading to reduced reuptake of norepinephrine and thus a higher extracellular concentration of the neurotransmitter at neuro-vascular or neuro-epithelial synapses. This would increase norepinephrine stimulation in the ciliary epithelium, putatively resulting in decreased aqueous humor formation. Further and unique among glaucoma medications, Rhopressa is also claimed to reduce episcleral venous pressure. This latter effect, demonstrated most recently in an animal study,12 may allow Rhopressa to consistently reduce IOP, even in patients with normal to mildly elevated baseline IOPs. The manufacturer previously announced that in a phase 1 study of 18 normotensive individuals (mean IOP 16 mm Hg; range 12 to 21 mm Hg) the drug reduced mean IOP to 11 mm Hg, a reduction of just over 30%.

These additional mechanisms beyond ROCK inhibition require further confirmation in animal and human studies.

Rhopressa reportedly demonstrated a useful IOP-lowering effect in a phase 2b clinical trial completed in 2013. Mean IOP reduction was 5.7 and 6.2 mm Hg, respectively, on days 28 and 14; the mean IOP-lowering effect was consistent regardless of the patients’ baseline pressures. In the first phase 3 registration clinical trial (Rocket 1 study) comparing once daily Rhopressa with twice-daily timolol, however, Rhopressa failed to meet the primary endpoint of non-inferiority to timolol in patients with a baseline IOP ranging from above 20 mm Hg to below 27 mm Hg. Further analysis of Rocket 1 results indicates that, had the high end of the baseline IOP range be set 1 mm Hg lower, at 26 mm Hg, Rhopressa would have shown non-inferiority at all time points and numerical superiority over timolol at the majority of time points. A second phase 3 registration clinical study (Rocket 2) is ongoing, and the FDA has agreed to reset the high end of the primary endpoint range to include patients with a baseline IOP ranging from above 20 mm Hg to under 25 mm Hg. The previous endpoint range of above 20 mm Hg to under 27 mm Hg will be a secondary endpoint range.

Roclatan, a fixed combination of Rhopressa and latanoprost, may be more effective because it encompasses all currently known IOP-modifying parameters: aqueous humor formation, uveoscleral outflow, conventional outflow, and episcleral venous pressure. The phase 3 clinical trials of Roclatan have yet to begin, but phase 2b data suggests that this putatively quadruplaction agent has the potential to be very effective.12

Rhopressa and Roclatan are not the first cytoskeletal agents—nonselective adrenergic agonists, such as epinephrine, presumably lower IOP by modifying the cytoskeleton in the trabecular meshwork cells. Epinephrine and related agents used to be a common treatment for glaucoma, but they are no longer used because of local and potentially systemic side effects. In Japan, a ROCK inhibitor known as ripasudil has been in clinical use for about a year. That agent demonstrates modest but sustained IOP-lowering effects, and, most recently, was shown to provide additive efficacy in combination with timolol or latanoprost.13,14 Nor are Rhopressa and Roclatan likely to be the last cytoskeletal agents that we will see: second-generation ROCK and norepinephrine transporter inhibitors are now in preclinical development.

ADENOSINE RECEPTOR AGONISTS

Like nitric oxide and ROCK inhibitors, adenosine receptor agonists act specifically on the trabecular meshwork. It is thought that adenosine-mimetics lower IOP by enhancing the aqueous outflow via the conventional pathway, although precisely how has not been fully elucidated. For outflow facility to increase significantly, clearly some kind of physical change must occur in the juxtacanalicular region of the trabecular meshwork and the inner wall of Schlemm’s canal. Even so, questions remain about what exactly these changes are and how such changes can be brought about by activation of adenosine receptors. Stimulation of the A1 adenosine receptor in the trabecular meshwork causes a meaningful improvement in metabolic activity there which helps to clear the pathway for the aqueous humor to flow out of the eye (lowering IOP). This metabolic activity takes the form of an increase or upregulation of proteases (such as Protease A or matrix metalloprotease-2 [MMP-2]) that digest and remove accumulated proteins that, in a glaucomatous eye, can block the healthy flow of aqueous humor from the eye. This metabolic activity is a naturally occurring process that is enhanced by treatment with trabodenoson. It is believed that this process does not radically change the way that the trabecular meshwork controls eye pressure.

Trabodenoson, a highly selective adenosine type 1 receptor agonist, is a first-in-class drug entering phase 3 clinical trials. In phase 2 trials, trabodenoson monotherapy significantly reduced IOP in patients with glaucoma and ocular hypertension.15 Its IOP-lowering efficacy, after 28 days of treatment, was found to be in the range of the prostaglandins.16

THE HOME RUN

Assuming they make it to market, these novel therapeutic agents will not necessarily displace our existing drugs. As with any new agent, how well these treatments work and how well they work together in real world conditions amongst many thousands of patients remains to be seen. That said, any novel medication that can reduce the therapeutic burden for patients should have a positive impact on glaucoma management.
An ocular hypotensive medication that could reliably reduce IOP to 10 mm Hg in virtually every patient without undue side effects would undoubtedly become the treatment of choice and change the landscape of medical and surgical glaucoma therapy, but that ideal medication is still nowhere in sight. Until that goal is reached, the aims of developing new ocular hypotensive glaucoma drugs will continue to be: greater efficacy, greater convenience.

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Measuring IOP: The Technology and Its Limitations

James C. Tsai, MD, MBA

The science behind IOP measurement and our understanding of what IOP means has evolved in irregular/intermittent intervals over the past half century. With new IOP measuring technology, I believe that we are on the brink of a new era.

Glaucoma management hinges on clinicians’ ability to assess and preferably quantify the pressure inside the eye from a position outside the eye, a dilemma that has, over the decades, spurred the development of a wide array of IOP measuring strategies and tools. The current gold standard IOP measuring device, the Goldmann applanation tonometer (GAT), was developed in the 1950s and replaced Schötz tonometry, an indentation tonometer invented in 1905. GAT is based on the Imbert-Fick law, which holds that “the pressure inside a sphere filled with liquid and surrounded by an infinitely thin membrane can be measured by the counterpressure that just flattens that membrane.”1-2 Armand Imbert (1850-1922) and Adolf Fick (1829-1901), working independently in France and Germany, respectively, in essence expanded upon Isaac Newton’s observation that “if you press a stone with the finger, the finger is also pressed by the stone.”

Applied to eye, the Imbert-Fick model is perhaps less a “law” than a guideline, an incomplete (some would say flawed) description of IOP biomechanics.3 It fails to account for multiple parameters that may vary from one patient to the next, including corneal thickness and elasticity and biomechanical properties of the intraocular fluid and the posterior globe.2,3 Accordingly, experts have questioned the accuracy of Goldmann tonometry (that is, the closeness of GAT-measured IOP to the actual pressure inside the eye at the time of measurement), since it was created using the Imbert-Fick model and presupposes parameters related to the cornea.1

Yet, despite its limitations, Goldmann tonometry remains the standard against which new IOP measurement techniques are assessed, even as technology has evolved and broadened our means for assessing IOP in a wide array of patient types. The recent introduction of continuous IOP monitoring (see discussion below) promises to provide a more complete IOP picture and could very well revolutionize glaucoma management as we know it.1 Here we present a limited review of available IOP measuring tools, discuss their indications and limitations, and look at what’s on the horizon.

REFERENCES

CORE CONCEPTS
● There are multiple contact and noncontact devices for IOP measurement, each of which has advantages and disadvantages.
● Contact methods generally require anesthesia and pose a slight risk to the patient.
● Contact applanation involves flattening the cornea; irregular corneal topography as well as naturally occurring variations in corneal parameters can reduce the accuracy of IOP measurement with these devices.
● Dynamic contour tonometry is not as influenced by corneal shape and thickness but may be difficult to perform.
● IOP is influenced by circadian rhythms, stressors, exercise, Valsalva maneuver, adherence to therapy, and likely other as yet unidentified factors.
● 24 hour IOP monitoring may afford a new window into IOP, its influences and implications.
CONTACT APPLANATION TONOMETRY

Goldmann Tonometry As a group, application techniques flatten the convex surface of the cornea into the shape of a small disc or plane, then use the force required or other mechanical parameters to calculate IOP. The GAT is the most widely used tool for approximating IOP in patients with glaucoma and glaucoma suspects. Goldmann tonometry requires a high level of expertise and carries a slight risk of corneal abrasion or infection. The technique requires application of topical anesthesia and fluorescein, and the tip that applanates the eye must sterilized between patients.1

There is a level of subjectivity inherent in Goldmann tonometry, as different investigators may judge the visual endpoint with some variability. Thus, comparing GAT measurements taken at different clinics or by different practitioners has to be seen as an imperfect comparison. Nor is the GAT designed to account for central corneal thickness variability—the device assumes an approximately 550 micron thick central cornea, despite significant variability in the population. Other variables, including astigmatism and amount of fluorescein applied, can also introduce error.1

Perkins Tonometry The GAT is limited to use in individuals who can sit upright and cooperate at the slit lamp. A portable version—the Perkins applanation tonometer—works similarly to the GAT and is comparably accurate.4,5 It is equipped with an internal counterbalance mechanism that allows for handheld use in the supine patient, making it well suited for children.1

Tono-Pen® The Tono-Pen® (Am- etek, Inc.) is a popular lightweight handheld contact tonometer that is particularly useful with children or uncooperative patients. Its tiny plunger/strain gauge construction allows for a microzone of contact between the device and eye; so it can be used on areas adjacent to the central cornea in patients with irregular corneal surfaces.5 Although easy to use, like the Goldmann and Perkins devices, corneal parameters that deviate from the norm can introduce error and compromise accuracy.6,7 As a contact method, the Tono-Pen requires topical anesthesia and a moderate level of technical training and skill to perform. Disposable covers are used to maintain sterility between patients.1

Pneumotonometry Pneumatic tonometry is a contact applanation technique that captures IOP values over time via a floating pneumatic sensor or piston that is placed on the anesthetized cornea. Accuracy is variable compared with the GAT; however pneumotonometry plays an important role in IOP measurement among patients with abnormally shaped corneas.6,8

Dynamic Contour Tonometry Dynamic contour tonometry detects pressure via a contour-matched piezoresistive sensor embedded in the tonometry tip that eliminates the need for corneal flattening. This reduces the influence of corneal parameters (eg, corneal curvature, central corneal thickness), which are highly variable within the general population.5,9-11 Since IOP is detected over a very brief time, artifacts introduced by the cardiac cycle and ocular pulse pressure are eliminated and accuracy enhanced.5

Some consider dynamic contour tonometry more accurate and precise than applanation tonometry methods.1 In a prospective study involving patients with and without glaucoma, dynamic contour tonometry was shown to yield measurements 4 mmHg higher than Goldmann applanation tonometry and to be less influenced by central corneal thickness.13 Performing dynamic contour tonometry has a steeper learning curve than most other methods.1,5

NONCONTACT METHODS

Noncontact, or air puff, tonometry methods use a rapid air pulse to flatten the cornea and an electrical sensor to measure the induced corneal change. There are no components that contact the eye, so risk of injury or infection is reduced, sterilization is not needed between patients, and there are no disposable covers or other consumables to purchase. Noncontact methods require no anesthesia or fluorescein, and operation of the unit is fairly straightforward.1 Since results are less accurate and reliable compared with other tools, noncontact tonometry is generally reserved for screening.12

RECENT TECHNOLOGIES

Ocular Response Analyzer The Ocular Response Analyzer (ORA) is a noncontact method notable for its inclusion of measurements of corneal viscoelastic properties, including corneal hysteresis and corneal resistance factor.10 The ORA provides two IOP measurements: one correlated with Goldmann tonometry and the other, a “corneal-compensated IOP” that adjusts the reported IOP by factoring in the other corneal biomechanical properties measured by the instrument.

Rebound Tonometry A new IOP measuring tool, the rebound tonometer (iCare Pro Rebound Tonometer®), is a portable contact IOP measurement device that can be used without anesthesia owing to the fast recoil speed of a fine magnetic ballistic probe that contacts the cornea. Velocity of the rebounding probe correlates with IOP.1 Studies indicate good but imperfect correlation with Goldmann and dynamic contour tonometry.14-16 In my experience, the IOP accuracy of rebound tonometry falls between the Goldmann/Perkins and Tono-Pen.

Rebound tonometry is useful as an alternative to noncontact methods for screening and as a second-line handheld IOP monitor in children and others who cannot use the slit lamp. It is also promising as a self-monitoring device in select patients.17,18

OTHER METHODS

Transpalpebral The Diaton device is a small handheld instrument that is placed against the external skin of the upper eyelid while the patient maintains a downward gaze in a seated or reclined position; a small probe rebounds against the lid and estimates the IOP through the eyelid.1 Accuracy is not as good as with some of the other techniques, however transpalpebral tonometry makes sense in some circumstances as a screening tool.19


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Digital tonometry, palpation with the index finger directly on the closed eye, is useful in patients with artificial corneas. Although notoriously unreliable, one may be able to ascertain the difference between a normal, soft, or hard-feeling eye.

CONFOUNDING FACTORS

Since IOP fluctuates throughout the day and is influenced by multiple variables, it is helpful to obtain multiple readings, preferably at different times during the day and night. A single IOP measurement is like an 8-second movie clip; with only one or two clips, one may get a distorted idea of what is happening in the film. But as clips are added, a more complete story may start to emerge. During office hours, IOP typically peaks in the morning or early afternoon; however sleep studies show that a majority of glaucoma patients experience prolonged nighttime IOP peaks as well.20

One of the most controversial topics in glaucoma today is the relationship between IOP fluctuation and the risk for glaucoma progression. The significance of elevated peak IOP, mean IOP, or short-term or long-term IOP range remains unclear.21 One possible theory is that frequent and/or wide fluctuations in IOP increase the eye’s metabolism of ATP, thereby causing physiological changes that place undue stresses on the optic nerve. In support of this theory, concentrations of extracellular ATP in the aqueous humor of patients with primary chronic angle-closure glaucoma were elevated 14-fold higher than in control subjects.22

Psychological factors may also influence IOP and confound its measurement. Psychological stress in the form of computer-based arithmetic tests were shown to significantly increase IOP measured by Goldmann tonometry in healthy subjects.23 In a separate retrospective review, our group compared IOP measurements obtained within 30 minutes of visual field testing (VFT) with measurements taken at neighboring visits that were not preceded by VFT.24 We pondered whether VFT might induce low-grade stress and if that might have a bearing on IOP (eg, effect of cortisol release). Indeed, we were able to demonstrate a slight but significant increase in IOP when the measurement followed VFT that was independent of other variables. When it becomes available, continuous IOP monitoring may be useful in mapping particular stressors in affected individuals and identify patients who might benefit from lifestyle-modification or stress-reduction therapies.

CONTINUOUS MONITORING

Twenty-four hour IOP monitoring used to require that patients spend the night in a sleep lab and endure hourly or every-other-hour awakenings for testing. Newly developed continuous IOP monitors promise to bring IOP assessment into the 21st century and provide a more comprehensive and patient-friendly experience. The SEN-SIMED Triggerfish® contact lens sensor (Sensimed AG) is a disposable silicone contact lens with an embedded microchip able to detect changes in corneal contour and circumference as they occur in real time for up to 24 hours. IOP is believed to be correlated with contour changes which allow calculation of IOP. Since contour change is believed to be correlated with IOP, contour change can be used to determine IOP.20 So far, IOP as measured by continuous monitoring contact lenses has shown good correlation to IOP measured by pneumotonomometry.25

AN IMPLANTABLE IOP MONITOR

A German first-to-market implantable IOP monitoring device has been successful at the 1-year mark post-implantation (Figure 1).26 The ARGOS study included six patients with well controlled glaucoma who were scheduled to undergo cataract surgery; during that surgery they underwent implantation of a telemetric IOP sensor in the ciliary sulcus. Researchers report that home self-monitoring was feasible and measurements from the internal sensor correlated well with GAT measurements taken at office visits. The device has been well-tolerated except for transient anterior chamber inflammation and pupillary distortion attributable to the product.

Widespread uptake of continuous 24-hour IOP monitoring with a contact lens or long term continuous monitoring with an implantable device has the potential to augment many aspects of glaucoma care, including early detection, individualized treatment, prevention of progression, as well as risk factor detection and modification. Medication compliance is a major challenge in glaucoma care. The ability to “watch” IOP fluctuations throughout the day could reveal gaps and motivate patients toward greater medication adherence.20

CONCLUSION

The large assortment of available technologies for measuring IOP can lead to confusion. The most reliable monitoring comes when a clinician well versed in a handful of IOP measurement options uses the instrument best suited to the individual patient on a consistent basis. The addition of continuous IOP monitoring to the glaucoma specialist’s toolbox may eventually be game-changing.

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REFERENCES


TSAI References continue on page 8
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6. Strutton DR, Walt JG. Trends in glaucoma sur-

7. Tanna AP, Rademaker AW, Stewart WC, et al. Meta-analysis of the efficacy and safety of alpha2-

8. Pfeiffer N; European Latanoprost Fixed Combina-


11. Tanihara H, Inoue T, Yamamoto T, et al; VOYAGER study group. A randomised, controlled comparison of latanoprostene bunod and latano-
prost 0.005% in the treatment of ocular hyperten-


13. Farhood QK. Comparative evaluation of in-


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1. Which of the following IOP measuring technologies relies on corneal applanation?
   A. Perkins
   B. Contour deformation measuring contact lens
   C. Pneumotonometry
   D. ORA

2. Which of the following statements about PGAs is correct?
   A. They reduce IOP to the very low teens in the majority of patients
   B. They lower IOP by improving trabecular outflow
   C. They have been associated with a decrease in the rate of penetrating drainage surgeries
   D. They are no longer widely used in the US and other developed countries

3. Which of following glaucoma medications lower IOP by decreasing aqueous humor formation?
   A. Beta-blockers
   B. Alpha-2 agonists
   C. Cholinergic agonists
   D. Both A and B

4. Which of the following is true of non-contact tonometry?
   A. No fluorescein is required
   B. It is more accurate than Goldmann tonometry
   C. It requires use of topical anesthetic
   D. All of the above are true

5. Why have timolol/PGA combinations failed to gain FDA approval?
   A. Solubility issues prevent their formulation in the same bottle
   B. The added benefit of timolol is minimal compared to PGA alone
   C. There is no need: patients can just use a drop of each
   D. All of the above

6. Continuous IOP monitoring with a contact lens sensor or other device may one day be used to:
   A. Improve adherence to medications
   B. Pinpoint stressors that aggravate ocular hypertension
   C. Study the impact of IOP fluctuations on disease progression
   D. All of the above

7. Which of the following mechanisms may contribute to IOP reduction by increasing outflow facility at the trabecular meshwork?
   A. Inhibition of Rho kinase
   B. Inhibition of norepinephrine transporters
   C. Inhibition of adenosine receptors
   D. All of the above

8. Which of the following statements best characterizes the Imbert-Fick Law?
   A. It emerged after two decades of collaboration between Imbert and Fick
   B. It describes the relationship between stress, cortisol, and IOP fluctuation
   C. It provides the basis for Goldmann and Perkins applation tonometry
   D. It offers a complete description of corneal biomechanics

9. Which of the following new drugs acts on the trabecular meshwork?
   A. Latanoprostene bunod
   B. Rhopressa
   C. Trabodenoson
   D. All of the above

10. In the ARGOS study of the implantable IOP monitoring device, which of the following was NOT observed?
    A. Patients were unable to self-monitor IOP
    B. Monitor removal was required in a third of patients
    C. Monitor readings failed to correlate with Goldmann tonometry
    D. The anterior chamber remained free of inflammation in all patients in the first weeks following surgery

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