

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Eyedrops After Cataract Surgery: Costs and Prescribing Patterns

May 2020

Zafar et al. looked at the costs and prescribing patterns for eyedrops after cataract surgery and estimated the savings of replacing brand drugs with generic or therapeutic options. They found that, in 2016, eyedrops were prescribed to 88% of Medicare patients who had cataract surgery. The total cost of these drugs exceeded \$167 million during the study period, and brand products accounted for more than 75% of this amount. Substituting therapeutic or generic alternatives could have saved up to \$118 million, said the authors.

For this retrospective cross-sectional study, the researchers evaluated Medicare Part D claims for patients who underwent cataract surgery in 2016. Outcomes were the cost of eyedrops used postoperatively, patient and physician factors linked to higher costs, and the potential savings of lower-cost options. For substitution, the most commonly prescribed generic medication in each drug class was used. For example, the authors considered generic ketorolac tromethamine as the alternative to nonsteroidal anti-inflammatory drugs (NSAIDs).

Of the 591,733 people who underwent cataract surgery that year, post-operative drops were prescribed for 520,688 (88%). Brand drugs accounted for 57.5% of the prescription volume and 76.5% of the total costs. Mean medication costs were \$228 for those who underwent one operation and \$324 for those who had two. The most commonly prescribed drugs were antibiotics (89%), steroids (86%), and NSAIDs (66%).

Results of the cost analysis showed that using generic and therapeutic alternatives could have saved as much as \$118 million, or 70% of total costs. In regard to patient factors, higher drug costs were associated with being older, being female, and being black, Asian, or Hispanic.

Physician factors linked to higher costs included being female, practicing 10 or more years, and practicing in a metropolitan area.

The authors concluded that in the absence of clinical evidence favoring brand products, less expensive drugs offer a viable opportunity to improve the value and cost of care after cataract surgery. They acknowledged that studies are needed to compare the effects of different combinations of eyedrops to prevent such conditions as cystoid

macular edema, rebound iritis, and dry eye syndrome.

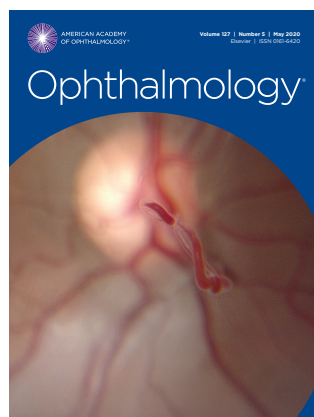
Cost-Utility Analysis of Glaucoma Medication Adherence

May 2020

Could a personalized team-based approach to glaucoma management—including certified patient coaches— increase notoriously low medication adherence rates? If so, would such interventions be cost-effective from the societal perspective? Newman-Casey et al. modeled costs and time to blindness for patients with optimal versus poor adherence to glaucoma medication. They found that sticking to prescribed treatment regimens could improve quality of life years (QALYs), with just a small increase in lifetime health care costs.

In an earlier study, the authors suggested that a team-based approach might boost patients' adherence to a treatment plan. For this cost-utility analysis, they used Monte Carlo micro-simulations with Markov tracking over one-year increments and a hypothetical cohort of patients. These theoretical patients all had mild glaucoma (less than -6 dB of mean deviation), were enrolled at 40 years of age, and continued until they turned 100 or had died. (Probability of death was based on U.S. Census data.)

At enrollment, the cohort's mean deviation was -1.4 ± -1.9 dB in the better eye and -4.3 ± -3.4 dB in the worse eye, reflecting baseline values of the U.K. Glaucoma Treatment Study, which also provided data for estimating



glaucoma progression and treatment effect on visual deficits. Adherence rates were derived from four-year U.S. claims data, and the probability of disease worsening each year (accumulated -0.8 dB loss) was based on the Glaucoma Laser Trial and the Tube Versus Trabeculectomy studies. Direct and indirect health costs were assessed at each “stage” of disease, as were societal costs from vision loss. Main outcomes were cost and QALYs of medication adherence.

After 10,000 iterations per strategy, the quickest progressions to blindness in one eye for consistently adherent and nonadherent patients were 23 and 19 years, respectively. Total health care costs (≤ 60 years after diagnosis) were \$62,782 for adherent patients and \$52,722 for those who did not adhere to their medication protocols. During the same period, nonadherent patients lost a mean of 0.34 QALY relative to adherent patients, yielding a cost-effectiveness ratio of \$29,600 per QALY gained.

According to the authors, assuming a willingness to pay \$50,000 per QALY gained, self-management counseling services that improve medication adherence would be highly cost-effective. They noted that more studies using national estimates of glaucoma are needed. (*Also see related commentary by Florent Aptel, MD, in the same issue.*)

Real-World Efficacy of Anti-VEGF Drugs for DME

May 2020

Although aflibercept and ranibizumab have shown efficacy in clinical trials of diabetic macular edema (DME), less is known about their benefit in clinical settings. To address this, **Bhandari et al.** analyzed registry data for patients with DME and found that both drugs were efficacious in treating the condition. Aflibercept produced slightly better anatomic outcomes, as well as greater visual improvement in patients with poorer baseline visual acuity (VA).

The observational Fight Retinal Blindness! registry was mined for data on patients with DME treated in various countries from Dec. 1, 2013,

COVID-19 in the Journals: Selected Links

Ophthalmology

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through June 1, 2018. Treatment choice (aflibercept or ranibizumab) and visit frequency were individualized for each patient by the practitioner. The main outcome was mean change in VA from baseline to month 12.

The sample included 383 treatment-naive eyes of 291 patients; initial treatment was aflibercept in 217 eyes and ranibizumab in 166. At baseline, the ranibizumab group was older (mean difference, $+2.7$ years), and the aflibercept group had lower mean VA (mean difference, -3.1 letters) and thicker maculae (mean difference, $+26 \mu\text{m}$); differences were not significant.

By 12 months, VA gains were similar for the study arms if baseline VA was ≥ 69 letters (Snellen 20/40 or better): 1.4 for aflibercept and 0.4 for ranibizumab ($p = .4$). However, more of the patients treated with aflibercept gained ≥ 10 letters. If mean baseline VA was ≤ 68 letters (20/50), VA gains were 10.6 and 7.6 letters for aflibercept and ranibizumab, respectively ($p < .01$).

Reduction in central subfield thickness (CST) was greater with aflibercept than ranibizumab, regardless of initial VA: At 20/40, CST reductions were -85 and $-55 \mu\text{m}$, respectively ($p < .01$); at 20/50 vision, reductions were -148 and $-102 \mu\text{m}$, respectively ($p < .02$).

The median number of injections during the year of treatment was eight for aflibercept and six for ranibizumab ($p = .13$). Few patients switched treatment, and the loss to follow-up was greater in the aflibercept group (21% vs. 9%; $p < .01$). Most switches were from ranibizumab to aflibercept.

The authors' observations are consistent with results of pivotal clinical trials and meta-analyses of these drugs. However, in this study, aflibercept led to greater visual gains in patients with poor baseline VA as well as larger CST reductions, which may be ascribed to more advanced disease at presentation, said the authors. They recommend longer-term observational studies of intravitreal therapy for DME.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Impact of Cataract Surgery on DME in VISTA and VIVID

May 2020

In a post hoc analysis of two phase 3 studies, **Moshfeghi et al.** set out to evaluate the impact of cataract surgery in patients who had been treated with anti-VEGF injections or laser for their diabetic macular edema (DME). They found that the incidence of cataract surgery was similar in both treatment groups—and that patients in both groups experienced improvements in best-corrected visual acuity (BCVA).

This secondary analysis was conducted in 54 patients (11 = laser treatment; 43 = intravitreal injections) who participated in the VISTA and VIVID trials and underwent cataract surgery during the initial study period. In these trials, more than 800 patients received aflibercept 2 mg every four weeks, aflibercept 2 mg every eight weeks after five monthly doses, or laser through 100 weeks.

Rescue treatment was also conducted during VISTA and VIVID, but those who received such treatment before cataract surgery were excluded from this follow-up study.

Main outcome measures for this secondary analysis were BCVA and central retinal thickness (CRT), as measured by spectral-domain optical coherence tomography. The results indicate that the cumulative incidence of cataract surgery did not depend on treatment group assignment ($p = 0.2174$).

With regard to pre- and post-op

BCVA and CRT, at the last study visit before cataract surgery, BCVA was 62.2 letters and CRT was 342 μm in the laser control patients, versus 56.9 letters and 301 μm in the aflibercept group. At the first visit following surgery, BCVA had improved to 73.5 letters in the laser cohort and to 67.2 letters in the aflibercept patients. In contrast, CRT worsened slightly after cataract surgery, with measurements of 364 μm in the laser group and 359 μm in the aflibercept group. —*Summary by Jean Shaw*

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Visual Impairment and Eye Disease in Chronic Kidney Disease

May 2020

As the worldwide prevalence of chronic kidney disease (CKD) increases, so have efforts to investigate the link between CKD and visual impairment (VI) and major eye diseases. In one of the first large studies to assess this issue in U.S. adults, *Zhu et al.* confirmed a significantly higher prevalence of VI and major eye diseases in participants with CKD than in those without the disorder, as well as links between CKD and VI and major eye diseases after adjustments for sex, smoking status, diabetes, hypertension, and other variables.

For this cross-sectional analysis, the researchers extracted data for noninstitutionalized, nationally representative U.S. civilians 40 years old and older from the National Health and Nutrition Survey (2005 to 2008). CKD was defined as estimated glomerular filtration rate <60 mL/min/1.73 m², and VI was defined as corrected visual acuity worse than 20/40 in the better eye. Data from questionnaires or retinal photographs were used to categorize major eye diseases, including any ocular disease (defined as presence of cataract surgery, age-related macular degeneration [AMD], glaucoma, or any retinopathy) and any objectively determined ocular disease (defined as AMD, glaucoma, or any retinopathy).

The analysis included 5,518 partici-

pants (mean age, 56.9 years). Of these, 839 had CKD. VI was much more common in those with CKD (7.7% vs. 1.1% without CKD; $p < .001$), and the risk of major eye diseases was up to five times higher in the CKD group. After adjustment for multiple confounding variables, participants with CKD had 1.65- to 2.34-fold higher odds of VI (odds ratio [OR], 2.01), any ocular disease (OR, 1.65), any objectively determined ocular disease (OR, 1.52), any retinopathy (OR, 1.70), and diabetic retinopathy (OR, 2.34). The ORs for cataract surgery, AMD, and glaucoma were not significant. Stratification by diabetes status showed that CKD was linked to VI in patients with diabetes and to any ocular disease in patients without diabetes.

The authors speculated that the relationships between CKD and VI and major eye disease observed in their study reflect common risk profiles (such as age, diabetes, hypertension, or obesity) and pathogenesis (such as atherosclerosis, oxidative stress, or inflammation). They suggested that further research on the pathogenesis of eye and renal disease could lead to development of viable treatments for both. Meanwhile, they stressed the importance of early ophthalmic screening of patients with CKD.

Algorithm for Assessing and Treating Microbial Keratitis

May 2020

To guide early management of corneal ulcers, *Ung et al.* devised a modified version of the 1-2-3-Rule, which they termed 1-2-3-ACT (for 1-2-3 Assessment, Culture, Treatment). They found that 1-2-3-ACT lessened the need for culturing after initial deferral in cases with borderline microbial keratitis (MK) and reduced unnecessary cultures among the least severe cases. In turn, this lowered costs.

This retrospective study involved patients with MK treated during two periods: group I (2013 to 2015) had clinician-led decision-making, while those in group II (2016 to 2018) were managed per 1-2-3-ACT.

The original 1-2-3-Rule has three

parameters for performing corneal cultures: 1) ≥ 1 cell within the anterior chamber; 2) infiltrate ≥ 2 mm; and 3) infiltrate edge within 3 mm of the cornea center. To capture atypical bacterial, fungal, and *Acanthamoeba* infections, the authors added “and/or ≥ 2 adjacent lesions” to the second criterion. Patients who met at least one criterion received fortified antibiotic therapy. The main study outcome was any vision-threatening complication.

The primary analysis set included 665 patients in group I and 767 in group II. A vision-threatening complication developed in 12.9% of group I (median follow-up, 67 days) and in 11.2% of group II (median follow-up, 60 days) ($p = .51$). No meaningful differences in complication rates were found among patients who met zero, two, or three parameters. However, for those with just one parameter, it was more common in group II to culture at presentation (67.7% vs. 54.6% for group I; $p = .006$) and to start fortified antibiotics at that time (53.9% vs. 29.7% for group I; $p < .001$). The number of vision-threatening complications also was significantly lower in group II (1.8% vs. 9.7% for group I; $p = .001$). Among patients who did not undergo culture at presentation, culturing was later required for 5.1% of group II and 13.4% of group I ($p = .001$). The proportion of patients who had tissue sampling despite not satisfying any criterion was lower in group II (8.5% vs. 23.9%; $p < .001$).

Multiple logistic regression showed that all three 1-2-3-ACT criteria were strongly and independently associated with clinical outcome, even in a bootstrapped cohort of 10,000 theoretical patients, indicating that the model may be viable for various clinical settings.

The findings support tissue culturing and antibiotic use at presentation if a corneal ulcer meets at least two of the 1-2-3-ACT criteria. Judging disease severity can be challenging in patients who have just one criterion, said the authors; they emphasized that early aggressive treatment of borderline cases should reduce the risk of vision-threatening complications.

—*Summaries by Lynda Seminara*

Waterless Scrub Techniques May Curb Costs

April 2020

Although some health organizations recommend alcohol-based hand scrubbing as presurgical antisepsis, water-based scrub techniques are still common at some hospitals and other surgical facilities. Javitt et al. looked at the potential cost savings of a switch to waterless scrub for a large ophthalmic surgical center. They found that omitting water from the presurgical hand-sanitization process could save millions of dollars each year for modern health care facilities, while conserving valuable resources.

For this study, the authors tested the flow rate of industry-standard scrub sinks by running water for the time recommended by the World Health Organization, and the water produced was collected and weighed. This procedure was performed three times at each OR scrub sink, and the mean value was calculated. In addition, the authors reviewed cost data. Main outcome measures were the quantity of water used during aqueous scrubbing and the cost differences between alcohol- and water-based scrubs per OR per year.

The average water consumption was found to be 15.9 L in a two-minute period. Hence, substituting alcohol-based scrubs could save 61,631 L of water per OR each year, for a yearly savings of \$277 in water costs. For each OR, the annual cost of alcohol-based surgical scrub was \$1,083 less than that of aqueous soap applied from wall-mounted dispensers and \$271 less than the price of soap-infused scrub brushes. Overall, adopting a waterless scrub technique could save \$280,000 to \$348,000 annually for each OR.

The researchers pointed out that the savings in water alone is “eclipsed by savings in supplies as well as staff and facilities resources” and noted that they hope that this study’s findings may improve environmental and financial awareness in health care institutions.

Simulated Heading of Soccer Ball Impairs Neuro-Ophthalmologic Function

April 2020

The oculomotor system is sensitive to brain trauma, but the neuro-ophthalmologic response to subconcussive trauma is unclear. Using the King-Devick test (KDT) and oculomotor function as measured by the near point of convergence, Nowak et al. studied the impact of such injuries on ophthalmologic function and found that they indeed affect neuro-ophthalmologic function, at least in the short term.

For this randomized trial, adult soccer players were assigned to a heading group or a kicking group (controls). The heading group executed 10 head maneuvers with a soccer ball traveling at 25 mph. The kicking group followed a similar protocol but had foot contact with the ball rather than head contact. The authors used a triaxial accelerometer to assess head accelerations. Measurements of KDT speed, KDT error, and near point of convergence were taken at baseline (before heading or kicking) as well as 0, 2, and 24 hours after heading or kicking. The main outcome measure was the group-by-time interaction of KDT speed at hour 0 after heading or kicking. Secondary outcomes included KDT speed at 2 and 24 hours after ball contact, KDT error, and near point of convergence.

Of the 78 athletes (male and female) enrolled in the study, 11 withdrew voluntarily. The mean age of the remaining 67 participants was 20.6 years; 36 were in the heading group and 31 in the kicking group. The mean (standard deviation) peak linear acceleration and peak rotational acceleration per impact in the heading group were 33.2 (6.8) g and 3.6 (1.4) krad/s^2 , respectively. As expected, soccer kicking did not produce a detectable level of head acceleration. Both groups showed improvement in KDT speed (heading group: -1.2 [$p = .03$], -1.3 [$p = .05$], and -3.2 seconds [$p < .001$] at 0, 2, and 24 hours, respectively; kicking group -3.3 , -4.1 , and -5.2 [all $p < .001$] seconds at 0, 2, and 24 hours, respectively). The kicking group performed KDT faster than the

heading group at 0 hours (-2.2 ; $p = .001$), 2 hours (-2.8 seconds; $p < .001$), and 24 hours (-2.0 seconds; $p = .007$).

The authors concluded that the neural circuitry linking cognitive and oculomotor function seems vulnerable to acute subconcussive head. They added that further research may determine whether parameters used in this study could help in detecting subconcussive injury. (Also see related commentary by Nita Bhat, MD, Shruthi Harish Bindiganavile, MD, and Andrew G. Lee, MD, in the same issue.)

IOLs in Infants and Long-Term Visual Outcomes

April 2020

Does implantation of an IOL enhance long-term visual outcomes for infants who undergo unilateral cataract surgery? Lambert et al. performed a randomized study to address this question. Their findings showed that roughly 10 years following surgery, best-corrected visual acuity (BCVA) was no better if an IOL had been used as opposed to leaving the eye aphakic and correcting it later with a contact lens.

This multicenter randomized study included 114 infants with unilateral congenital cataract who had cataract surgery between 1 and 6 months of age, with or without primary implantation of an IOL. Visual outcomes were evaluated when the patients were 10.5 years of age. The primary outcome measure was BCVA according to the electronic testing protocol of the Early Treatment Diabetic Retinopathy Study.

Among the final analysis set of 110 patients, BCVA was excellent (logMAR 0.30 [Snellen 20/40] or better) in 22% of IOL-treated eyes and 27% of aphakic eyes. However, BCVA was inadequate (logMAR 1.00 [Snellen 20/200] or worse) in 44% of both groups. Results were similar in shorter-term studies of the same patients, at ages 12 months and 4.5 years.

The median BCVA for IOL-treated eyes was 0.89 (Snellen equivalent, 20/159; interquartile range [IQR], 0.38-1.38) and for aphakic eyes was 0.86 (Snellen equivalent, 20/145; IQR, 0.30-1.46). Although the difference between

groups was small, the estimate was imprecise (99% confidence interval, -0.54-0.47 for difference in medians).

Originally, the authors had hypothesized that BCVA would be better in the IOL group since those infants would have had at least partial correction at all times. Because they found no visual benefit, coupled with the fact that IOL-treated eyes are more likely to have visual axis opacity and require additional surgery, the authors no longer recommend routine use of IOLs for infants who require cataract surgery.

In summary, IOL implantation at the time of cataract surgery is neither beneficial nor detrimental to visual outcomes, the authors said. Based on the longitudinal consistency of results for these patients, the authors expect the visual outcomes to continue into adulthood, barring ocular injury or disease. The extent to which the findings may apply to less-experienced surgeons, or to patients whose families cannot afford contact lenses, should be factored into treatment decisions. (*Also see related commentary by Michael X. Repka, MD, MBA, in the same issue.*)

—Summaries by Lynda Seminara

Other Journals

Selected by Prem S. Subramanian, MD, PhD

Using AI to Differentiate Glaucomatous and Compressive Optic Neuropathy

British Journal of Ophthalmology
Published online Feb. 25, 2020

Lee et al. evaluated whether a novel deep learning (DL) classifier could discriminate between glaucomatous optic neuropathy (GON) and compressive optic neuropathy (CON). They found that their transfer learning-trained model accurately distinguished GON from CON and outperformed clinical diagnostic parameters.

The researchers' DL model uses ganglion cell-inner plexiform layer (GCIPL) and retinal nerve fiber layer (RNFL) maps obtained via spectral-domain optical coherence tomography (SD-OCT). For this study, they recruited their study population from

a Korean database. Bottleneck features from four images were integrated and used as training data for the classifier's deep neural network. Area under the curve (AUC) was calculated to validate and compare the performance of the DL classifier with that of standard diagnostic parameters, such as SD-OCT thickness profiles.

Overall, 80 patients with GON and 54 patients with CON were included, along with 80 and 81 SD-OCT image sets, respectively. Baseline characteristics were similar for the study groups. When discriminating GON from CON, the DL classifier achieved AUC of 0.990, sensitivity of 97.9%, and specificity of 92.6%. Moreover, it significantly outperformed conventional diagnostic parameters: temporal raphe sign (AUC, 0.804), superonasal GCIPL thickness (AUC, 0.815), and superior GCIPL thickness (AUC, 0.776); all $p < .001$. Assessment of heat maps—derived from RNFL deviation maps that highlighted OCT areas for which the DL algorithm was the best predictor—indicated that the model used clinically important information to interpret the images.

According to the authors, the DL classifier's discrimination of GON from CON, even if the clinical diagnosis was unclear, supports its potential to augment diagnostic accuracy and objectivity in ophthalmology. With additional training and a larger dataset, the DL model could be helpful when visual field defect patterns are equivocal.

Do Certain Dietary Fats Protect Against AMD?

Investigative Ophthalmology & Visual Science
2020;61(2):20.

Although the etiology of age-related macular degeneration (AMD) is believed to be multifactorial, evidence suggests that a poor diet and high cholesterol levels play a role in disease development and progression. Dietary fat consumption also has been implicated, but concordance is lacking on the specific type of fat. Roh et al. looked more closely at dietary fat intake and found a link between AMD and

high consumption of trans fat. Mono-unsaturated and polyunsaturated fatty acids (MUFA and PUFA) appeared to have a protective effect.

Participants in this cross-sectional study were at least 50 years old and had AMD based on color fundus photography. A U.S. cohort was recruited from January 2015 to July 2016, and Portuguese participants were recruited from a population-based study. A similar control group had no evidence of AMD. Patients completed a questionnaire to determine their energy intake of trans fat, saturated fat, MUFA, and PUFA during the preceding year.

The final analysis included 483 participants. Of these, 97 (20.1%) were controls, 90 (18.6%) presented with early AMD, 201 (41.6%) had intermediate AMD, and 95 (19.7%) presented with late AMD. Mean age was significantly higher for those with AMD, but otherwise the two groups were similar.

After multivariate adjustments, higher consumption of trans fat was found to correlate with AMD (odds ratio [OR], 2.36; $p = .0156$). In contrast, higher intake of PUFA and MUFA was inversely associated with AMD (OR, 0.25 [$p = .0063$] and 0.24 [$p < .0001$], respectively). No association was found for saturated fat. The analysis by stage showed that higher trans fat intake was common with intermediate AMD (OR, 2.26; $p = .0228$), but higher intake of PUFA and MUFA appeared protective of intermediate disease (OR, 0.2 [$p = .0013$] and 0.17 [$p < .0001$], respectively) as well as advanced disease (OR, 0.13 [$p = .02$] and 0.26 [$p = .004$], respectively). Omega-6 PUFA trended toward reducing the risk of intermediate AMD (OR, 0.30; $p = .0165$). The inverse relationship between MUFA and AMD was significant only for the Portuguese subset; this may reflect the composition of the Portuguese diet.

In addition to providing data on the various stages of AMD, this study showed that high intake of trans fat correlates with the presence of AMD, whereas PUFA and MUFA appear to offer protection. Omega-6 PUFA also seemed beneficial, but the authors urged more research into this relationship.

—Summaries by Lynda Seminara