Medication-related Ocular Surface Disorders Among Glaucoma Patients

Christophe Baudouin, MD, PhD

Eye drop preservatives prevent microbial contamination of the bottle but eventually affect the eye. Eye care providers should know the extent of the ocular surface risk of chronic exposure to preservatives and be prepared to modify therapy for medication intolerance, noncompliance, or in preparation for surgery.

Ocular surface disorders, including dry eye syndrome, are more prevalent among age-matched glaucoma patients (nearly 50%) compared with the general population (15%); and evidence indicates that years or decades-long exposure to topical ocular medication may be the chief culprit. Greater glaucoma severity, multitherapy, and longer disease duration have all been associated with increased rates of dry eye among glaucoma patients. Notably, ocular surface signs and symptoms are significantly more common among patients treated with topical medications that contain preservative compared with those taking preservative-free formulations (Figure 1). Many of these signs and symptoms resolve or lessen when preservative-free formulations are substituted for preserved formulations.4

WHY OSD MATTERS
Maintaining the health of the ocular surface is of more than minor importance in the care of glaucoma patients. First of all, regardless of cause, ocular surface disorders are associated with significant morbidity, often causing stinging, burning, irritation, and dryness and taking a toll on quality of life. The impact of dry eye on patients’ visual experience and comfort can go underappreciated by clinicians who take preservation of the optic nerve as their sole aim and responsibility. Irritation, foreign body sensation, photophobia, and other symptoms can seem to us a small price to pay for the chance to preserve eyesight. That may be true, but we owe it to our patients to consider the full range of their eye-related symptoms.

FIGURE 1  Major inflammation of the ocular surface in a patient receiving multiple anti-glaucoma medications over the long term. (Courtesy of Dr. Baudouin.)

Keep in mind that the substantial benefit of IOP-lowering medication—especially over the long-term—may feel somewhat abstract, remote, or intangible to patients. They often begin treatment as a matter of faith, with no outward signs of disease evident. Like the disease, treatment is beleaguered.

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by uncertainties: many patients will not lose vision irrespective of treatment, and a subset of less fortunate patients will suffer visual loss despite treatment. Compound these factors—the anxiety of an uncertain fate and the baseline gamble of lifelong treatment—with real-time, treatment-induced suffering, and standard of care becomes a considerably more complicated proposition.

Medication-related ocular surface side effects can contribute to dissatisfaction with treatment and noncompliance, limiting patients’ prospects for successful IOP control.5,6 Additionally, dry eye may influence quality of vision, causing intermittent blurred or unstable vision that may interfere with visual function and performance and as a consequence evaluation of glaucoma outcome. Side effects are among the most common reasons patients cite for discontinuing therapy, second only to insufficient understanding of the potential consequences of the disease.

The ocular surface also plays a role in surgical outcomes.7 Long-term exposure to antiglaucoma therapies has been associated with increased inflammatory cells (eg, fibroblasts, lymphocyte, and macrophages) and decreased goblet cells in conjunctival tissue, both of which can contribute to post-operative conjunctival fibrosis and compromise bleb functioning.5,6 Conversely, an uninfamed, scar-free conjunctiva is more likely to yield favorable outcomes.

TOXIC MECHANISMS

Chronic topical ocular antiglaucoma medication use may initiate ocular surface inflammation or exacerbate underlying ocular surface disease such as dry eye, meibomian gland dysfunction, or chronic allergy (Figure 2).6 Most formulations contain a preservative, the most common one being the quaternary ammonium benzalkonium chloride (BAK). BAK is used for its high antimicrobial potency, low antigenicity, and relative safety compared with mercury and other formerly favored preservative agents.5

Long-term exposure to BAK, however, is associated with cellular and tissue damage precipitated by a variety of mechanisms. In vitro studies show that BAK damages conjunctival and trabecular meshwork cells in cell culture by cytotoxic (eg, apoptosis and oxidative stress) and proinflammatory mechanisms; animal studies reveal trabecular meshwork damage due to BAK.5,9 As a detergent capable of permeating and disorganizing lipid membranes, BAK disrupts the lipid layer of the human tear film leading to evaporative dry eye. BAK has also been shown to reduce the density of goblet cells, which has the effect of reducing mucin produc-
tion—necessary for even distribution of tears across the ocular surface—which further deteriorates tear film function. Clinical studies comparing exposure to preserved vs preservative-free topical beta-blocking agents revealed that BAK exposure is indeed associated with greater tear film instability and disruption of corneal barrier function.

CUMULATIVE DAMAGE

Clinicians must be vigilant for tolerability issues beyond the limited parameters used in clinical trials, which typically exclude patients with underlying ocular surface disease and are performed over 6 to 12 months. Preservative-related ocular surface toxicity is cumulative, taking months to years to manifest, and it may be most severe among patients with advanced disease and those with ocular comorbidities.

All too commonly, eye care providers fail to consider medication effects among patients whose therapeutic regimen has been well tolerated in the past and remains unchanged, reasoning that medication intolerance is an early event and tolerance has been demonstrated. This is true for many forms of drug allergy, many cases of which present shortly after initiation; however, when taken over many years, medications must still be on the differential diagnosis for late-presenting symptoms.

While the volume of preservative in topical medication poses no clinically meaningful threat to the ocular surface in a single dose, repeated doses—particularly at frequent intervals—permit insufficient time for ocular cells to naturally regenerate between exposures. As a consequence, histological and biochemical micro-insults will overwhelm the restorative capacity of the eye over time. Studies have shown that, among glaucoma patients, risk for ocular surface toxicity and/or dry eye severity increases with the following variables: increased number of preserved medications used, greater number of drops per day, duration of topical antiglaucoma medication use, and severity of glaucoma. Advanced age and past drug regimen change were also markers for more severe ocular surface disease.

REDUCING CYTOTOXIC EXPOSURE

Minimizing exposure to inflammation-inciting agents—including preservatives—is integral to the management of glaucoma, particularly when ocular surface disease is evident. It is a common mistake to fuel the fire by adding another topical agent (eg, antiinflammatory or artificial tear) that contains BAK. A recent study of glaucoma patients showed that among the 40% who were also being treated for ocular surface disorders, half of those prescribed artificial tears were given a preservative-containing product.

For patients taking multiple antiglaucoma agents, the simplest way to reduce exposure to preservatives is the use of fixed combination drops, which essentially cuts the preservative exposure in half without compromising IOP-lowering potency. Fixed-dose combination antiglaucoma medications are more widely available in Europe, where the collective consciousness around the dangers of preservatives (in medications, foods, etc) is generally higher compared with the US. Preservative-free medications dispensed in single dose vials are available in Europe for most classes of antiglaucoma agent; studies have shown that switching patients to preservative-free antiglaucoma agents improves signs and symptoms of ocular surface disease.

Preservative-free therapy may be standard of care in 10 to 15 years with increased awareness of BAK-induced ocular toxicity and the importance of ocular surface health. Demand, uptake, and marketing of preservative-free medications might follow a trajectory similar to that of daily disposable contact lenses: first seen as an impractical novelty reserved for select patients, daily disposables quickly became preferred by prescribers and patients for their safety and gentleness on the ocular surface.

Some patients, however, find small aliquots of medication in single-dose vials cumbersome to handle and dispense; further, their currently low market share keeps the costs high in the US. As of today, two preservatives have been developed as less toxic alternatives to BAK for use in ophthalmic agents: Purite® and SofZia™. Purite®, a stabilized oxychloro complex, is associated with fewer conjunctival and corneal toxic effects compared with BAK in...
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animal studies and fewer ocular surface symptoms in clinical studies.16 Purite-preserved brimonidine ophthalmic solution is formulated as Alphagan-P® (Allergan, Parsippany-Troy Hills, N.J). Travatan Z® (Alcon, Fort Worth, TX) is the first prostaglandin analog preserved with SofZia, a boric acid, propylene glycol-based preservative that also demonstrates reduced conjunctival and corneal toxicity compared with BAK.17

ROLE OF SURGERY

Laser trabeculoplasty procedures and minimally invasive glaucoma surgeries (MIGS) can reduce patients’ reliance on preservative-containing topical ophthalmic treatments. Reciprocally, preparing patients’ ocular surface for surgery is important for optimal results and post-surgical IOP control. In my experience, the process of preparing the ocular surface for surgery—reducing or stopping toxic preserved medications and tackling ocular surface inflammation—can have the unexpected but welcome benefit of eliminating the need for surgery in the first place; with the ocular surface healed, patients sometimes tolerate and respond better to medical therapy alone.

CONCLUSION

Preservatives protect the bottle but do not protect the eye. BAK is known for its cumulative ocular cytotoxicity via multiple mechanisms; alternatives are badly needed. Until that time, reducing exposure to BAK (and increasing demand for combination agents and affordable preservative-free options) can delay and potentially prevent preservative-related ocular surface disease.

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Secondary Glaucoma: Beyond Exfoliative and Pigmentary Glaucoma

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The less common forms of secondary glaucoma can often be the most difficult to treat, due to the involvement of underlying systemic disease, the complexity of ocular tissues involved, and the challenging differential diagnosis.

Secondary glaucomas include a broad and clinically diverse group of conditions that share an identifiable cause of increased intraocular pressure (IOP), which can ultimately result in optic nerve damage and loss of vision. The most common forms of secondary glaucoma are exfoliative and pigmentary glaucoma, distinguished by the deposition of fibrillary material (in the former) and pigment granules (in the latter) in the drainage angle of the eye. In either case, these depositions cause impaired aqueous fluid outflow and increased IOP. The less common forms of secondary glaucoma include neovascular, uveitic, childhood, traumatic glaucoma, and iridocorneal endothelial syndrome. Improvements in techniques to evaluate the optic nerve and retinal nerve fiber layer, such as optical coherence tomography (OCT), and improvements in techniques to evaluate the angle, such as ultrasound biomicroscopy and anterior segment OCT, are important for early diagnosis and treatment of these conditions.
NEOVASCULAR GLAUCOMA

Neovascular glaucoma is characterized by a hypoxic retina, which is commonly associated with an underlying systemic disease such as diabetes melitus or vascular occlusive disease. The most common etiologies are diabetic retinopathy and central retinal vein occlusion, but also include other retinal venous obstructive diseases, carotid artery obstructive disease, and, less commonly, central retinal artery occlusion, rhegmatogenous retinal detachment, uveitis, radiation retinopathy, and choroidal melanoma.

The retinal response to this localized hypoxic and/or injured environment is an upregulation of proangiogenic proteins including platelet-derived growth factor, transforming growth factor-α, β, tumor necrosis factor-α, hepatocyte growth factor, matrix metalloproteinase 3, matrix metalloproteinase 9, erythropoietin specific gene encoded protein, and vascular endothelial growth factor (VEGF).

The aberrant growth of new, poorly patent vessels in the retina causes vitreous hemorrhage, macula edema, retinal fibrosis, and, should they extend to the anterior chamber of the eye, neovascularization of the iris or anterior chamber angle. This can result in peripheral anterior synechiae, possible closure of the trabecular meshwork, prevention of normal aqueous fluid drainage from the anterior segment of the eye, elevated IOP and, if untreated, glaucomatous optic neuropathy.

The eyes of patients presenting with neovascular glaucoma are often extremely red and painful, indicating a requirement for immediate attention since there is a high risk of significant vision loss. The management strategy for this condition is at least two-fold. First, it is necessary to provide immediate attention to the localized pathology by administration of IOP-lowering medications (such as prostaglandin analogues, beta-blockers, cholinergic agonists or carbonic anhydrase inhibitors) and steroids to reduce local inflammation. Second, collaboration with a retinal specialist or an experienced general ophthalmologist is often required to address the neovascular component of the condition. Pan-retinal photocoagulation is effective in decreasing the retinal oxygen demand and associated ischemic drive for angiogenic factor transcription, even in the early rubecosis (pre-glaucoma) stages of the disease, when IOP levels may still be normal, through to the open-angle and closed-angle stages of glaucoma, when IOP is elevated.

A relatively recent advancement that has revolutionized the management of ocular neovascular pathologies is the use of intraocular anti-VEGF therapy. The most commonly used anti-VEGF used for neovascular glaucoma is off-label bevacizumab (Avastin). Both ranibizumab (Lucentis) and aflibercept (Eylea) have yet to be indicated for this condition, although both drugs are indicated for treatment of diabetic macular edema and retinal vein occlusion, which often underlie neovascular glaucoma. The effectiveness of anti-VEGF agents for the treatment of neovascular glaucoma still requires investigation through randomized, controlled trials to inform clinical practice decisions. The administration of anti-VEGF injections prior to glaucoma surgery (traditionally trabeculectomy or insertion of a drainage implant ) has the added benefit of reducing the risk of bleeding during surgery, which may further contribute to blocking the drainage angle in the eye.

A third possible step in the management of neovascular glaucoma involves collaboration with the patient’s general physician to address the underlying systemic disease (such as diabetes or hypertension) that may be implicated in the etiology of certain neovascular glaucoma pathologies.

UVEITIC GLAUCOMA

This range of inflammatory disorders, which occurs in up to 20% of patients with chronic uveitis, is one of the most challenging to manage due to the younger age of patients (thus requiring lifetime management), high IOP with acute elevations, and varied response to treatment relative to other glaucomas.

Often resulting in more intense optic nerve damage and visual impairment, uveitic glaucoma can be divided into open- and closed-angle types: the former is characterized by mechanical obstruction of the trabecular meshwork with inflammatory cells, proteins, debris, fibrin or inflammatory precipitates; the latter is characterized by synechial closure, neovascularization of the chamber angle, seclusion pupillae with subsequent appositional angle closure, or, less commonly, ciliary body forward rotation causing angle closure (such as observed in Vogt-Koyanagi-Harada syndrome).

In many of the uveitic glaucoma cases, the observed ocular inflammation is associated with an underlying disease such as sarcoidosis, spondyloarthropathies, inflammatory bowel disease, Pachychoroid iridocyclitis, herpes simplex, zoster virus, Lyme disease, Vogt Koyanagi-Harada disease, cancer, Behcet’s disease, sarcoidosis, spondyloarthropathies, inflammatory bowel disease, Pachychoroid iridocyclitis, herpes simplex, zoster virus, Lyme disease, Vogt Koyanagi-Harada disease, cancer, Behcet’s disease.
juvenile idiopathic arthritis, and syphilis. However, there are cases in which the underlying disease and the etiology of the uveitis is not apparent in spite of detailed laboratory investigations.

Some racial differences in the presentation and prevalence of uveitis, which may ultimately predispose glaucoma, have been observed; for example, sarcoidosis is more common in Blacks than Whites in the United States, and Blacks more commonly have anterior segment involvement, while Whites more commonly have posterior segment involvement. Similarly, racial differences in response to treatment for uveitic glaucoma (such as steroid implants and trabeculectomy) have been postulated.

One form of open-angle uveitic glaucoma is Posner-Schlossman syndrome, or glaucomatocycitic crisis. This typically unilateral condition, which presents mostly in younger patients between the ages of 20 and 50, is characterized by recurrent episodes (ranging from a few hours to a few weeks) of self-limiting, mild, non-granulomatous anterior uveitis. The observed inflammatory changes within the trabecular meshwork that cause impaired aqueous outflow and markedly elevated IOP are postulated to be mediated by prostaglandins. The etiology of Posner-Schlossman syndrome is not clear, but it is often associated with cytomegalovirus and herpes simplex virus; other proposed etiologies include autonomic dysfunction, abnormal vascular response, and developmental abnormalities.

Diagnosis of Posner-Schlossman syndrome can be difficult since the subtle clinical features of the disease, namely low-grade uveitis and the short-lived nature of each attack, can mimic a variety of other ocular disorders. These include acute angle-closure glaucoma, chronic angle-closure glaucoma, Fuchs heterochromic iridocyclitis, and primary open-angle glaucoma.

Posner-Schlossman syndrome responds well to a combined regimen of an antiinflammatory and antiglaucoma drug(s), although in rare cases the condition can be chronic, and recurrent episodes of inflammation may lead to long-term glaucomatous damage. Potential IOP elevations caused by steroids in steroid-responsive patients may complicate the treatment of Posner-Schlossman syndrome, in which case a topical nonsteroidal antiinflammatory drug helps to control the inflammation. In rare cases where uncontrolled IOP may result in progressive optic nerve damage and visual field loss, glaucoma filtration surgery may be required.

Another form of open-angle uveitic glaucoma is Fuchs heterochromic iridocyclitis. Presenting as a triad of anterior uveitis, heterochromia, and cataract, the condition is characterized by chronic but mild inflammation that is not associated with any scar tissue. Eyes are often asymptomatic and respond well to IOP-lowering medication and corticosteroid drops, but filtering surgery may be needed to control the IOP.

The condition may be associated with cytomegalovirus; in such cases, patients tend to be male, older at diagnosis, and have nodular endothelial lesions.

The uveitic glaucomas can be difficult to differentially diagnose. The typical management strategy for uveitic glaucoma is to treat the inflammation component aggressively with corticosteroids and then taper off once the inflammation and IOP are controlled. In refractory cases, it is important to take an interdisciplinary approach that includes a uveitis specialist and a rheumatologist to address not only the ocular inflammation and elevated IOP but also the underlying systemic inflammation. Often, these patients will require glaucoma surgery (eg, trabeculectomy); however, care must be taken to avoid the complication of hypotony, in which the IOP is lowered too much, causing further ocular damage.

FIGURE 1 Uveitic Glaucoma Diagnosis Chart

Potential IOP elevations caused by steroids in steroid-responsive patients may complicate the treatment of Posner-Schlossman syndrome, in which case a topical nonsteroidal antiinflammatory drug helps to control the inflammation. In rare cases where uncontrolled IOP may result in progressive optic nerve damage and visual field loss, glaucoma filtration surgery may be required.

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CHILDHOOD GLAUCOMA

These childhood pathologies, which can be categorized as either primary childhood glaucoma (primary congenital glaucoma or juvenile open-angle glaucoma) or secondary childhood glaucoma (associated with non-acquired ocular abnormalities or systemic diseases, acquired conditions, and post-cataract surgery) constitute some of the greatest clinical challenges for pediatric ophthalmologists and glaucoma specialists. All conditions are
TRAIUMATIC GLAUCOMA

Typically related to accidents or physical alterations, approximately 85% to 90% of traumatic glaucoma cases present in males. Following the traumatic event, risk factors for developing glaucoma are increased age, poor visual acuity at presentation, perforating rather than penetrating injury, lens dislocation, vitreous hemorrhage, presence of an intraocular foreign body, and post-trauma cataract surgery. The condition develops secondary to the disturbance of the trabecular meshwork and direct inflammatory scarring, or the accumulation of inflammatory debris, lens particles, coagulated blood components, and red blood cells from hyphema or vitreous hemorrhage. Angle recession or synechial angle closure may develop, resulting in the impediment of aqueous fluid drainage and elevated IOP.

Prevention of glaucoma development following open-globe injury is critical. An important aspect of management is to appreciate that trabecular meshwork scarring may develop some significant period of time after the traumatic event—in some cases only after years—thus it is recommended that patients be followed up annually at a minimum, particularly for those patients who have had significant eye trauma. Where traumatic glaucoma develops, IOP-lowering medications are the primary treatment, although many patients will require surgery, such as trabeculectomy or insertion of a glaucoma drainage device, to address the tissue damage.

Traumatic glaucoma can also be induced as a consequence of surgery, such as cataract or retinal surgery; associated bleeding can block the trabecular meshwork, causing elevated IOP. For this reason, it is very important to avoid bleeding during surgical procedures and, if bleeding does occur, to ensure that all blood is evacuated. Since antiinflammatory steroid medications are commonly prescribed for up to 3 to 4 weeks after many surgical procedures, caution should be taken to monitor the patient for drug-related elevations in IOP; switching to less potent antiinflammatory medications may be indicated.

IRIDOCORNEAL ENDOTHELIAL SYNDROME

This spectrum of secondary angle-closure diseases includes corneal endothelial abnormalities, unilateral glaucoma, and iris stromal abnormalities. The three main conditions that comprise this group are essential iris atrophy, Cogan Reese syndrome, and Chandler’s syndrome (Figure 2). All share a common etiology of viral infection, typically by herpes simplex or Epstein-Barr virus. The condition is characterized by unabated growth of a corneal endothelium membrane over the anterior surface of the iris and the angle structures resulting in a distorted iris, peripheral anterior synechiae and angle closure, leading to elevated IOP and glaucoma.

The management of iridocorneal endothelial syndrome can be challenging for ophthalmologists. The administration of IOP-lowering medication and glaucoma surgery (such as mitomycin C-augmented trabeculectomy) is usually indicated. Glaucoma surgery, however, may not be effective in the long-term, as the membrane often regrows, requiring multiple surgeries to achieve a successful outcome. In refractory cases in which trabeculectomy or shunt surgery have repeatedly failed, cyclophotocoagulation is indicated.

CONCLUSION

In summary, secondary glaucomas outside of the more common exfoliative and pigmentary types comprise a clinically diverse and often complex group of pathologies that, in many instances, are associated with an underlying systemic condition. Due to the complexity of these conditions, an interdisciplinary approach involving collaboration with other medical specialists is often the best strategy for effective treatment management. The potential for patients to develop glaucomatous optic neuropathy and severe or, at worst, irreversible vision loss, makes it critical for ophthalmologists to diagnose and treat these unusual pathologies in a timely manner.

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1. Which of the following is an advisable option for patients with long-standing glaucoma and medication-related ocular surface disease?
   A. Switch to combination agent
   B. Switch to preservative-free treatment
   C. A and B
   D. None of the above are advisable

2. Recommended strategies for treating uveitic glaucoma include:
   A. Co-management of the patient with a rheumatologist in refractory cases
   B. High potency anti-inflammatory medications for the majority of cases
   C. Performing glaucoma filtration surgery in almost all patients presenting with Posner-Schlossman syndrome
   D. Anti-VEGF therapy for refractory cases

3. Which of the following factors have NOT been demonstrated to contribute to or correlate with cumulative ocular surface damage among glaucoma patients?
   A. Number of medications
   B. Iris color
   C. Glaucoma severity
   D. Duration of treatment

4. Secondary glaucomas are always characterized by:
   A. The deposition of pigment granules within the trabecular meshwork which impacts aqueous outflow
   B. An underlying disease etiology such as diabetes, vascular occlusive disease, uveitis and viral infection
   C. Impediment of aqueous outflow via the drainage angle secondary to an underlying disease, congenital development or an event
   D. High intraocular levels of VEGF

5. Childhood glaucomas:
   A. Are always secondary to congenital malformation of the drainage angle
   B. Are commonly treated with licensed medications in dosage formulations that are pharmacologically appropriate for the age and body mass of juvenile patients
   C. Can be treated effectively by trabeculotomy and goniotomy in instances where the disease is primary congenital glaucoma
   D. Are commonly associated with the herpes simplex virus in instances where the disease is juvenile open angle glaucoma

6. Which type of conjunctival cell is reduced by exposure to BAK?
   A. Goblet cells
   B. Lymphocytes
   C. Fibroblasts
   D. Macrophages

7. Neovascular glaucoma:
   A. Develops most commonly secondary to radiation retinopathy and choroidal melanoma
   B. Is associated with the upregulation of VEGF, transforming growth factor-α, β and PDGF
   C. Is always associated with increased HbA1c levels
   D. Can be treated effectively with on-label bevacizumab and ranibizumab

8. Which of the following is NOT a reason to prioritize the ocular surface in glaucoma management?
   A. Compliance
   B. Quality of life
   C. Potential need for surgery
   D. All are reasons to prioritize the ocular surface

9. Which of the following is NOT used in a currently available antiglaucoma medication?
   A. Purite
   B. BAK
   C. Mercury
   D. SofZia

10. The condition iridocorneal endothelial syndrome:
    A. Comprises three conditions: Cogan Reese syndrome, Chandler’s syndrome and Fuchs heterochromic iridocyclitis
    B. Is difficult to differential diagnose as there is no distinct clinical presentation for the subgroup of conditions
    C. Is commonly associated with viral infection, most typically by herpes simplex or Epstein-Barr virus
    D. Commonly develops secondary to open globe injury

11. Extent to which the activity met the identified:
    Objective 1: 1 2 3 4 5
    Objective 2: 1 2 3 4 5
    Objective 3: 1 2 3 4 5
    Objective 4: 1 2 3 4 5

12. Rate the overall effectiveness of the activity:
    Related to my practice: 1 2 3 4 5
    Will influence how I practice: 1 2 3 4 5
    Will help me improve patient care: 1 2 3 4 5
    Stimulated my intellectual curiosity: 1 2 3 4 5
    Overall quality of material: 1 2 3 4 5
    Overall met my expectations: 1 2 3 4 5
    Avoided commercial bias/influence: 1 2 3 4 5

13. Will the information presented cause you to make any changes in your practice?  Yes  No

14. If yes, please describe:

15. How committed are you to making these changes? 1 2 3 4 5

16. Are future activities on this topic important to you?  Yes  No