Put several glaucoma specialists in a room and solicit opinions on just about any clinical issue and you are bound to receive multiple opinions on how to manage the problem. For example, a patient presents with shallow angles on van Herrick screening. What gonioscopic features would prompt you to perform a laser iridotomy? Would you perform a dark room provocative test to confirm your impression that the angle was potentially occludable? Do you perform a pharmacological challenge test before proceeding to prophylactic laser iridotomy? Would you order an ultrasound biomicroscopic test to confirm your impression? If you do decide that prophylactic laser iridotomy is indicated, what is the best surgical technique for achieving patency? Is there evidence to support a “best approach” to the patient with the narrow angle? In this chapter, we discuss how evidence-based medicine (EBM) can be used to provide the very best answers to questions such as these. This approach can be applied not only to glaucoma problems, but also to any clinical problem in medicine.

2.1 An Introduction to Evidence-Based Medicine

The era of evidence-based medicine is upon us. The Cochrane Collaboration (a large collection of volunteers who use a systematic approach to evaluate the efficacy and safety of medical interventions)\(^1\) has outmuscled the senior, distinguished, and experienced collection of dinner speakers (the so-called members of “eminence-based medicine”)\(^2\) whisked in from afar by pharmaceutical companies to tell us what is best for our patients. Today, even when “thought leaders” (a buzzword that finds its origin in the business world used to denote someone held in high regard because of his or her trendsetting ideas or the appearance of his or her names on mail-in surveys) are recruited to speak about a medical product by industry, continuing medical education guidelines dictate that they must provide a balanced and evidence-based presentation. Yet there is considerable confusion regarding EBM. An article in *Time* magazine stated that EBM was “a hard, cold empirical look at what works, what doesn’t and how to distinguish between the two.”\(^3\) This statement about EBM suggests that all patient problems have straightforward solutions and EBM helps find those solutions fairly readily. Clearly, we commonly encounter glaucoma problems that are not straightforward at all. For instance, should we commit a European-derived Caucasian male patient with thin corneas, intraocular pressure (IOP) in the high-teens, glaucoma-like discs, and unreliable visual field findings to medical therapy for glaucoma? The Ocular Hypertension Treatment Study (OHTS), a randomized control trial (RCT) comparing IOP-lowering therapy versus observation in the prevention of primary open-angle glaucoma (POAG) in patients with ocular hypertension (OHTN), found thinner central corneal thickness (CCT) to be a risk factor for conversion to POAG among patients with OHTN;\(^4\) but while our patient has thin CCT, his IOP is normal. The Barbados Eye Study\(^5\) found that thinner CCT was an independent risk factor for POAG in a population of African descent, where subjects had a spectrum of IOP ranging from normal to high; however, this patient is Caucasian, which raises the question of whether the data are specifically applicable to his situation. Furthermore, there are absolutely no data to suggest that such treatment would be cost-effective at this time. Finally, there are patient-specific issues that may make the answer to this question even more difficult to arrive at. For example, if the patient is 80 years old and has a pill-rolling tremor secondary to Parkinson’s disease and is already taking eight other oral agents for other systemic illnesses, then the physician may opt to observe the patient. On the other hand, if the patient is 53 years old, expresses anxiety about glaucoma blindness, and has a strong family history for the disease, then the physician may be inclined to initiate treatment.

Dr. David Sackett, often regarded as the father of EBM, defines EBM as “the conscientious, explicit and judicious use of current best evidence in making decisions about the
care of individual patients. EBM is a process and there is nothing cold and calculating about it. The process starts with a patient in your exam lane. Typically that patient has a clinical problem that cannot be answered by consulting an ophthalmology textbook or a single paper in the literature, unless that paper happens to be an EBM review on the topic. For example, a 45-year-old African-American female with a positive family history of glaucoma blindness presents with intraocular pressure (IOP) of 24 mmHg OU, central corneal thicknesses of 545 μm OU, and CDR = 0.4, OU. A standard automated perimetry test is performed and is reliable and normal in both eyes. Do we treat this patient? If we do treat her, what would be the best initial approach? First, we assemble what is called the “evidence cart.” Admittedly, the cart may not be loaded with items (as it might be if we were dealing with breast cancer or myocardial infarction), but the items that are there may be quite appropriate for that patient sitting in your exam lane. Then, we need to examine the quality of the evidence in that cart. Finally, we apply that evidence to our patient as best as we can, given the medical and nonmedical circumstances related to her case. Later in this chapter, we will demonstrate the EBM process in detail.

2.2 Evidence-Based Medicine: An Interesting Story

In the year 2000, a glaucoma specialist was asked to give a talk on basic eye emergencies directed to primary care physicians. For a glaucoma specialist with a tertiary level glaucoma referral practice, delivering a talk on this subject seemed like a relatively easy task. During the talk, the glaucoma specialist pointed out that the best way to manage a traumatic corneal abrasion was to instill an antibiotic ointment and Cyclogyl 1% drops Topically, pressure patch the eye, and follow-up with the patient the next day. A very clear rationale for this approach was provided: The antibiot provided coverage against microbial invasion of the corneal stroma during the time when there was a breach in the overlying epithelial barrier; the cycloplegic agent reduced uveal spasm induced by the highly innervated cornea; and the pressure patch immobilized the lid to allow corneal limbal stem cells to resurface the epithelial break and settle onto the underlying Bowman’s membrane. How could that possibly be the wrong way to manage garden-variety corneal abrasions? At the end of the lecture, one of the course attendees politely approached the glaucoma specialist and stated that he might not be practicing EBM and that most abrasions could be treated without patching. This sounded like heresy to the glaucoma specialist. After all, the patch made the patient comfortable, and theoretically it should enhance resurfacing of the cornea epithelial defect – it had to be the correct approach! That night, the glaucoma specialist did a literature search on the management of cornea abrasions, and to his amazement he found a meta-analysis published in 1998 synthesizing the results of five randomized clinical trials comparing the patch versus no patch approach to managing traumatic corneal abrasions. The meta-analysis concluded that there was no advantage to patching as long as the patient was treated with a topical antibiotic, topical cycloplegia, and topical nonsteroidal anti-inflammatory agent. In fact, two randomized clinical trials (RCTs) published after this systematic literature review reached similar conclusions. Of course, it did not mean patching corneal abrasions was akin to malpractice; but it did indicate that this glaucoma specialist who completed his ophthalmology residency in 1990 and was not treating corneal abrasions on a regular basis anymore did not stay up-to-date in the management of traumatic corneal abrasion. He was not aware that one could manage corneal abrasions without resorting to patching the eye prior to delivering a lecture of the subject in year 2000. Oh by the way, I was that glaucoma specialist and that was the “ah-hah” moment that sparked my interest in EBM.

2.2.1 The Evolution of Evidence-Based Medicine

While the origin of EBM can be traced back to medieval times, the trends in medical care that resulted in the current embrace of EBM can be traced back to the American Revolution, starting with a physician-signer of the Declaration of Independence, Dr. Benjamin Rush. Dr. Rush’s approach to disease was to zealously attack and conquer it. After all, it was this philosophy that allowed the colonists to ultimately prevail over a seemingly formidable British adversary. Unfortunately, there were no real tools to address most of the medical problems encountered; and the attacks fervently employed by Dr. Rush (limited exsanguinations, the induction of emesis, blistering, etc.) typically took a “one-size-fits-all” approach, without evidence that they actually helped patients. Ultimately Dr. Rush’s ardent medical philosophy was supplanted by the realization that most medical therapies of the time were largely ineffective. The highly influential Sir William Osler popularized this latter philosophy. His approach to disease can be summed up in one of his more famous aphorisms: One of the first duties of the physician is to educate the masses not to take medicines. Sir Osler, regarded as the father of modern medicine, stated that the role of the physician was to provide accurate diagnoses, prognoses, and palliative care for most conditions. Beginning
in the early 1940s, the field of medicine witnessed the antibiotic revolution, the introduction of chemotherapy agents, and the discovery of penicillin. These agents looked like miraculous substances compared to what treatments were available to address medical conditions in the early 1900s (see Morris for a historical account of the impact of antibiotic therapy in the 1940s). Nonetheless, initial enthusiasm for these new tools led to their indiscriminate and often ill-advised use that did not necessarily translate into clinical benefit for our patients. In the mid 1990s, Dr. David Sackett introduced the idea that we should evaluate the literature with an eye toward finding the best evidence to guide clinical decision-making. The relation between the degrees of intervention for medical illness as a function of time dating from the late 1700s to present is illustrated in Fig. 2.1.

### 2.2.2 Evidence-Based Medicine: Why Bother?

There are compelling reasons to use the EBM process in the delivery of health care. First, there is an increasing volume of evidence available to address clinical problems, and the EBM approach helps keep the clinician abreast of this evidence in a way that allows them to deliver the best care for patients. For example, a major innovation in managing patients with OHTN involves using risk calculators to assess the chance of developing POAG. An estimate of the risk can be an important factor in deciding whether an OHTN patient should be committed to medical therapy for glaucoma. Mansberger introduced the idea that we should evaluate the literature with an eye toward finding the best evidence to guide clinical decision-making. The relation between the degrees of intervention for medical illness as a function of time dating from the late 1700s to present is illustrated in Fig. 2.1.

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2.2.3 The Evolution of Glaucoma Care

Since EBM centers on using published evidence to guide clinical decision-making, it is useful to review how ophthalmic advances influenced our managerial approach to the glaucoma patient. It is difficult to treat a disease if you do not even know what type of condition it is. It is somewhat ironic that the word glaucoma has its origins in the Greek language and it roughly means “grayish gleam” – hardly a term associated with an optic nerve disease. It originally was a term referring to elderly people with seemingly white and quiet eyes and a dull appearance on external inspection that was associated with visual disability from multiple causes including mature cataract. Thus, prior to the invention of the ophthalmoscope by Hemholtz17 (before 1851), visual disability from glaucoma was frequently confused with other conditions. The postophthalmoscope era afforded the clinician an ability to inspect the optic nerve and identify a group of visually disabled people who had white and quiet eyes, relatively clear media, and excavated optic nerve heads. Palpation of the globes of many (but not all) of these patients suggested that the IOP was elevated (the Schiotz tonometer had not been invented yet). These observations established that glaucoma was an optic nerve disease, but the frequent association with a firm globe to palpation suggested that glaucoma was a condition of elevated IOP that produced pathologic optic nerve changes; it is now known that glaucoma can occur across a spectrum of IOP values that include those in the statistically normal range. Nonetheless, the invention of the ophthalmoscope allowed clinicians to direct IOP-lowering treatment to patients with pathologically cupped optic nerves and elevated IOP. Intuitively it made sense to lower IOP in these patients with the limited therapies available to achieve such an effect. No one dared to question that an RCT might be needed to confirm that patients would benefit from such treatment.

A clear understanding that glaucoma existed in an angle-closure form and an open-angle form was not apparent until after the gonioscope was embraced as an important diagnostic tool. The postgonioscopic era began around 1920 when Koepe and others perfected the technique of evaluating the filtration apparatus with the patient in the seated position.18 Ultimately, this technique allowed physicians to more accurately identify patients with angle closure glaucoma who would benefit from iridectomy. Interestingly, despite the clear-cut importance of gonioscopy in a glaucoma work-up, available evidence suggests that gonioscopy is relatively underutilized in the management of glaucoma patients today.19,20

Prior to the launch of timolol, ophthalmologists had fairly limited tools to lower IOP in glaucoma patients. The treatments available had either undesirable side-effect profiles or poor efficacy. Pilocarpine, which has reasonable efficacy and has been available for more than 130 years to treat glaucoma,21 requires frequent application and produces a constricted pupil. In younger patients, these drugs produced significant myopic shift because of induced accommodation of the lens, and in myopic patients, they would occasionally cause retinal breaks.22 Topical epinephrine had a slightly better ocular side-effect profile but limited efficacy. Systemic carbonic anhydrase inhibitors were available from 1954, but they exposed the patient to systemic side effects. The introduction of timolol in 1978 ushered in the golden age of the topical beta-blocker. Topical beta-blockers were welcomed with open arms because while they did have some systemic side effects, they were tolerable and these drugs provided acceptable efficacy with once-daily or twice-daily dosing. With relatively few published placebo-controlled masked trials using IOP lowering and safety parameters as the outcomes,23 timolol’s superiority over epinephrine and pilocarpine became apparent and it instantly became the first-line treatment for glaucoma. In this era, no one questioned whether topical beta-blockers should be used as a first-line agent for glaucoma unless there was a contraindication to using a beta-blocker.

The 1990s witnessed the polypharmacy era, characterized by a significant expansion of the pharmacological armamentarium in treating glaucoma. The drugs that were introduced (topical carbonic anhydrase inhibitors24, alpha agonists25, and prostaglandin analogs26) created more treatment options for glaucoma patients. In fact, prostaglandin analogs offered the possibility of once-daily dosing, the virtual absence of systemic side effects, and IOP-lowering superior to timolol. In the 1990s, the balance had shifted from having limited options for lowering IOP to having a confusing number of ways of dealing with glaucoma, especially when one considers that parallel advances in laser trabeculoplasty and guarded sclerostomy surgery threatened to rival medical therapy in the treatment of glaucoma. This time period shares some parallels to the 1940s in general medicine when multiple tools were available to address disease (see Fig. 2.1).

A dark cloud was building over the entire field of glaucoma sometime after the golden age of beta-blockers and just before the polypharmacy era when a public policy official (Dr. David Eddy) questioned whether many medical treatments for many diseases (his article did not specifically single out glaucoma treatment) were really benefiting patients.27 The glaucoma field was particularly vulnerable to this criticism because it narrowly focused on IOP as an outcome with precious few studies focused on whether our treatments preserved optic nerve structure and function. This shift in emphasis from considering IOP outcomes to vision-preserving outcomes ushered in the randomized clinical trial era of the 1990s. These trials help establish that lowering IOP helped to prevent development of POAG among patients.
with the OHTS and slow disease progression in those with early manifest open-angle glaucoma (the Early Manifest Glaucoma Trial). In order to refine which IOP-lowering modalities were best for our patients, other RCTs compared a medicine-first approach to laser-first (the Collaborative Laser Glaucoma Trial) and medicine-first to surgery-first (the Collaborative Initial Glaucoma Treatment Study) in managing open-angle glaucoma. These trials will be the subject of later chapters, but they can be summarized by stating that overall there is currently no clear-cut advantage to using one modality to lower IOP when compared with another for glaucoma. Nonetheless, I will demonstrate that the EBM process can be used to inform clinicians about the management of individual glaucoma patients.

What will the future hold for glaucoma care and how will EBM help shape it? To answer this question, it is important to hark back to the time before the “postophthalmoscope” era. Initially, we did not even know that glaucoma was a disease of the optic nerve. Today, POAG – the most common form of glaucoma in the Western world – is a condition that is described in terms of risk factors rather than pathoetiologic elements. Similarly, primary angle closure glaucoma (PACG) – a common form of glaucoma in the Eastern world – is also poorly understood at a fundamental level. Thus, the next wave in glaucoma management will stem from a more complete understanding of the combination of genetic and environmental factors that dictate the etiology of all forms of glaucoma. As the various combinations of genetic determinants and environmental influences that dictate disease are published and confirmed, they will become the basis for genotype-specific tailored therapies, which may presage the “individualized medicine era of glaucoma.” EBM will be useful to determine if novel genotype-specific strategies to treat glaucoma are superior to conventional approaches of managing the condition. Initially, genotype-specific strategies may not be embraced (initially, there was resistance to accept Schiotz tonometry as a replacement for finger palpation of the globe in the assessment of IOP), but RCTs will pressure physicians to adopt these approaches if they are truly superior to the way we practice currently.

In the interim, we will see modifications of the current ocular hypertension risk calculator and the emergence of new risk calculators that estimate the risk of developing glaucoma and the risk of progressing to more severe forms of the disease. Such knowledge will be based on a more complete understanding of the natural history of disease and how it is modified by current treatment. Such knowledge will, of course, be evidence-based. We will also see an increase in the use of meta-analysis to synthesize the rapidly accumulating evidence regarding our current glaucoma treatments. Meta-analysis is really a formal statistical approach to review the literature on a subject. First, the quality of the evidence is assessed so that only worthwhile reports are included. Then, statistical methods are applied to determine which studies from disparate centers can be combined. Models are then formulated to convert a series of small trials into a single large trial. The advantage of this approach is particularly apparent if some of the smaller trials actually contradict one another, or if the individual trials conclude that one treatment is similar to another, but each individual study is actually underpowered to detect any real difference between the treatments. For example, a meta-analysis of nine RCTs concluded that bimatoprost and travoprost are slightly more effective in lowering IOP than latanoprost. This finding is consistent with another meta-analysis of 13 RCTs that concluded that bimatoprost was superior to latanoprost in lowering IOP.

Nevertheless, more work is needed as still another literature synthesis has pointed out that no individual medical agent has been shown to preserve optic nerve function as measured by automated perimetry, and only beta-blockers have been shown to slow disease progression. The absence of such evidence does not mean that our current therapies are not effective at preserving vision, but more clinical research is needed to optimize our treatments for glaucoma.

2.3 The Evidence-Based Medicine Process

2.3.1 Formulation of a Clinical Problem

Assume a 70-year-old white female presented to your office today with difficulty driving at night. Your examination leads you to conclude that the patient’s symptoms are related to mild cataract formation, but an incidental finding was the presence of exfoliation precipitates in the anterior segment of both eyes, IOPs of 26 mmHg OD and 21 mmHg OS, and normal open angles on gonioscopy. Furthermore, the cup-disc ratio is 0.8 OD and 0.55 OS. On Humphrey visual field testing, there is a superior arcuate defect and inferior nasal step in the right eye and a shallow superior nasal step in the left eye. The Snellen acuity is 20/30 OU in both eyes. After you explain that cataracts were making it difficult to drive at night, the patient opts to defer cataract extraction because she was not critically disabled by her visual complaint. She was actually relieved to know the major source of her vision problem was potentially fixable. Nonetheless, she was not prepared to discover she had glaucoma. You inform the patient about the diagnosis of exfoliation glaucoma and, without much reflection on the matter, initiate treatment with travoprost 0.004% ophthalmic solution dosed one drop at bedtime in both eyes. The patient readily accepts this treatment; but in a quieter moment, you wonder whether such treatment was the optimized approach to her case. This moment of reflection represents the genesis of the EBM process: formulation of a
clinical question. In this case, the question is what is the best first-line treatment for this elderly lady with new-onset exfoliation glaucoma?

2.3.2 Assembling the Evidence Cart: From Textbooks to Systematic Reviews

After crystallizing a clinical problem based on a patient encounter, the next task is assembling the available evidence that addresses this particular issue. Your question really is: “If I am committing this patient to medical therapy, is travoprost really the best choice for her?” Stated another way: Is there a prostaglandin analog that is particularly effective for exfoliation glaucoma? The meta-analyses referenced in the last section indicating that travoprost and bimatoprost were superior to latanoprost did not stratify their results by open-angle glaucoma subtype (i.e., exfoliation glaucoma versus other types of glaucoma).32,33 This reformulation of the question assumes that medical therapy, as opposed to laser trabeculectomy or incisional surgery, represents the best initial approach to managing her condition – an issue we will return to later. Furthermore, in thinking about the answer to this question, we must also consider the ocular side-effect profile of each agent.

In general, there are many potential resources available to potentially address your patients’ problems, and oftentimes, these sources contain conflicting information. They include textbooks, “blue ribbon panels” convened by cost-conscious third-party payers, consensus panels handpicked by pharmaceutical companies, journal articles, online search engines such as PubMed, or online databases that search multiple articles and synthesize the literature on a particular subject. Where would you go first to find the answer to your question?

Thomas Kuhn in his highly influential treatise entitled, *The Structure of Scientific Revolutions*,35 points out that, “Textbooks aim to communicate the vocabulary and syntax of a contemporary scientific language.” For example, a typical glaucoma textbook is useful to learn the basics about exfoliation glaucoma and will address disease management in general terms, but it is unlikely to guide you on the specifics of optimum management of your 70-year-old lady with newly diagnosed exfoliation glaucoma. You may seek the assistance of the personal library of journal articles that you subscribe to and read faithfully every month, but it will become obvious very quickly that scouring them will not be a terribly efficient way to find the answer to your question. The logical way to address this problem is to use a general online search engine like PubMed to find studies that address your particular question. In order to use PubMed, your patient encounter, which has been transformed to a relevant clinical question, must be transformed again into “keywords” that can be searched. If we had used the keywords *therapy* for exfoliation glaucoma and will address disease management in general terms, but it is unlikely to guide you on the specifics of optimum management of your 70-year-old lady with newly diagnosed exfoliation glaucoma. You may seek the assistance of the personal library of journal articles that you subscribe to and read faithfully every month, but it will become obvious very quickly that scouring them will not be a terribly efficient way to find the answer to your question. The logical way to address this problem is to use a general online search engine like PubMed to find studies that address your particular question. In order to use PubMed, your patient encounter, which has been transformed to a relevant clinical question, must be transformed again into “keywords” that can be searched. If we had used the keywords *therapy* and *exfoliation glaucoma* (other synonyms such as pseudoexfoliation glaucoma should also be tried) on June 21, 2008, there would be 319 references and most of these would not be relevant to this patient’s individual clinical situation. In reviewing this list of publications, we find five articles36–40 that are relevant to our clinical problem.

While we were able to find relevant information about our patient problem on PubMed, this is a somewhat time-consuming process. Is there a better way? The short answer is: not at the current time. Theoretically, the Cochrane Collaboration, an organization that provides up-to-date reviews on healthcare interventions in all areas of medicine, would be the ideal shortcut to get the answer to our patient-related question. Essentially, the Cochrane Collaboration searches for articles that perform the kind of literature search outlined above and summarizes the results in one article. At this time, a search using keywords *therapy* and *exfoliation glaucoma* alone did not yield any relevant results since no one has written an evidence-based review on the subject of optimum medical therapy for exfoliation glaucoma. In fact, the keyword *glaucoma* will yield a list of 86 meta-analytical articles on glaucoma in all.

2.3.3 Evaluating the Quality of the Evidence

Once the evidence cart for our clinical question has been assembled, we must examine the quality of that evidence. Certainly, if the five articles we found related to our patient were of poorly designed studies, then they would not be useful in guiding our decision-making process with respect to our patient. Cochrane reviews would ordinarily do the quality analysis for us, but again there are no such reviews related to our patient. It is recommended that when the evidence cart is assembled that one looks for the RCTs first, as they represent a gold standard level of evidence for any particular intervention. Then one needs to ask the following questions about these RCTs:

- Is the allocation to treatment arms random and, if possible, are the investigators masked to the interventions employed in the study?
- Are the baseline attributes of each treatment arm clearly stated? A particularly useful study design incorporates a crossover paradigm. In crossover studies, each patient serves as his or her own control and is exposed to each treatment after an adequate washout period. This addresses any difference in baseline attributes between groups and also serves to increase the power of the study.
- Is the study adequately powered to find a difference between treatment groups? Look for a mention of an
A priori power calculation in the methods section of the paper.

- Do the authors present an intention-to-treat (ITT) analysis? There is an important dictum in clinical trials: once randomized, always analyzed. Patients who switch treatment arms or who drop out are always analyzed in the groups they were allocated to at the time of randomization.
- Are withdrawals adequately reported and is the dropout rate reasonable (below 10%)?
- Is there industry sponsorship for the study? Industry sponsorship does not mean the study is tainted but it is important to take note of such sponsorship. It is almost certain that industry sponsorship creates a certain publication bias, whereby results that do not show a product in a favorable light are suppressed. New rules about registering clinical trials with the Food and Drug Administration (FDA) are trying to minimize such publication bias.

Let us look at the evidence we have accrued for our particular clinical question. All five studies are randomized clinical trials. The majority of studies involve Greek nationals, raising some concerns about the generalizability of the data to other populations. A summary of the quality of each article is provided in Table 2.1. Each article gets a point each if the masking is judged to be adequate, power calculations are provided, an intent-to-treat analysis is performed, the withdrawal rate is less than 10% (somewhat arbitrary), and industry support is declared. If the study is free from industry sponsorship, then a score of two points is given. More formal grading systems of papers can be performed, but since the purpose is not to perform a meta-analysis but to get a rough idea that the data in the paper are believable, a simplified grading system looking for these particular attributes is recommended. For the evidence, we have accumulated for our question, we have five studies with quality scores ranging from 1 to 6 on a scale of 0 to 6, with most studies having scores of 4 or more. Therefore, the quality of the evidence that we have accumulated is generally quite good.

### 2.3.4 Applying the Evidence to Our Case

After assessing the overall quality of the evidence assembled, it is important to ascertain the outcome of these studies. All of these studies looked at either diurnal IOP or IOP at one time point as the main efficacy outcome. There are no data regarding whether any of the treatment options available to treat our particular patient are more effective in preserving vision. In looking at the IOP outcomes, it is also important to distinguish between statistical significance and clinical significance. Regulatory agencies state that differences in IOP of 1.5 mmHg or more constitute clinical significance, although there is no evidence to refute the notion that smaller differences in IOP that are statistically significant may also be clinically significant. The side-effect profile of the various treatment options should also be considered in making a decision about our patient.

In summary, the evidence (summarized in Table 2.2) indicates that for exfoliation glaucoma, both travoprost and bimatoprost produce statistically significant lowering of diurnal IOP versus latanoprost, but the differences in IOP lowering are less than 1.5 mmHg. Latanoprost produced significant reduction in diurnal IOP versus timolol that was greater than 1.5 mmHg. Two studies indicated that fixed combination timolol 0.5%—dorzolamide 2% was superior to travoprost and latanoprost in terms of IOP lowering, but the difference was <1.5 mmHg. Furthermore, one of these studies did not receive a high quality score and the other only used 10 am IOP as the outcome of interest. From a clinical perspective, it might not be a good idea to start newly diagnosed patients on fixed combination therapy because it exposes a newly diagnosed patient to the side effects of two classes of medicines. Overall, no major safety issues were raised in any of these studies. So the decision to start the patient on travoprost was reasonable, but one could not be faulted for starting any of the prostaglandin analogs for our newly diagnosed exfoliation glaucoma patient.

Is it reasonable to consider laser trabeculoplasty or trabeculectomy for our patient? There are no RCTs designed to compare medical therapy to laser trabeculectomy.

### Table 2.1 Quality scores for randomized clinical trials assessing the effectiveness of medical therapy for exfoliation glaucoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Masking adequate?</th>
<th>Study design</th>
<th>Power adequate?</th>
<th>ITT analysis performed?</th>
<th>Withdrawal rate</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Konstas et al36</td>
<td>Yes</td>
<td>Cross-over; N=40</td>
<td>Yes</td>
<td>Yes</td>
<td>5%</td>
<td>None provided</td>
</tr>
<tr>
<td>Konstas et al37</td>
<td>Yes</td>
<td>Cross-over; N=129</td>
<td>Yes</td>
<td>Yes</td>
<td>5%</td>
<td>Provided</td>
</tr>
<tr>
<td>Parmaksiz et al38</td>
<td>No</td>
<td>Parallel; N=50</td>
<td>Not assessed</td>
<td>Yes</td>
<td>16%</td>
<td>Unclear</td>
</tr>
<tr>
<td>Konstas et al39</td>
<td>Yes</td>
<td>Parallel; N=103</td>
<td>Yes</td>
<td>Yes</td>
<td>5.5%</td>
<td>Partial</td>
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<tr>
<td>Konstas et al40</td>
<td>Yes</td>
<td>Cross-over; N=65</td>
<td>Not assessed</td>
<td>No</td>
<td>16%</td>
<td>None provided</td>
</tr>
</tbody>
</table>

*ITT* intent to treat
(performed with either the argon or selective laser unit) in exfoliation glaucoma. Nonetheless, one can refer to the Glaucoma Laser Trial, which showed that argon laser trabeculoplasty was as effective as medical therapy (during the golden age of beta-blockers) in the treatment of open-angle glaucoma.30 Thus, if there are unusual circumstances that prevent adherence or if the patient and the physician simply prefer a laser-first approach after an appropriate informed consent process, it is reasonable to proceed with laser trabeculoplasty to manage the case. With respect to surgery, the Collaborative Initial Glaucoma Study evaluated whether glaucoma filtration surgery or medicine is the optimal initial approach to manage newly diagnosed OAG.31 The interim study results showed that visual acuity and visual field outcomes were similar in both groups after 4 years of follow-up, prompting the study investigators to conclude that physicians should not change their practice patterns of routinely not offering patients surgery as the first option to manage OAG.

### 2.3.5 The Basic Calculus of Evidence-Based Medicine

A typical RCT will report the main outcomes of a study and discuss the side effects associated with one intervention versus another. For example, in the OHTS, which assessed whether prophylactic treatment of OHTN prevented people from developing POAG, it was reported that the rate of conversion from OHTN to POAG was reduced from 9.5 to 4.5% with ocular hypotensive therapy after 5 years.29 These data suggest that lowering IOP in OHTN helps people generally, but can we get a deeper understanding of the trial results? Furthermore, how do we use these data to guide treatment decisions for individual glaucoma patients? The terms **absolute risk reduction**, **relative risk reduction**, and **the number needed to treat**41 help us assess exactly how effective ocular hypotensive therapy is in reducing conversion from OHTN to POAG.

The **absolute risk reduction** (ARR) is the difference in outcome rate between treatment option 1 and treatment option 2 in a clinical trial. In the OHTS, 9.5% of patients with OHTN who were observed converted to a diagnosis of POAG, while only 4.5% of those under treatment converted to the same diagnosis. The ARR is 9.5–4.5 or 5%. The **relative risk reduction** (RRR) is the proportional reduction in event rates (failure to respond to treatment) between treatment option 1 and treatment option 2 in a clinical trial. In the OHTS, treatment did not completely prevent patients with OHTN from developing glaucoma. In fact, treatment resulted in a 4.5/9.5 or 50% RRR. Most diseases have low rates of occurrence; therefore, RRR tends to inflate the apparent benefit of any given treatment and ARR tends to underestimate it. Thus, another term has been introduced into the calculus of EBM to put the relative effectiveness of treatment into perspective, and that term is the **number needed to treat** (NNT). The NNT is the number of patients who need to be treated in order for one patient to receive benefit (such as the prevention of one case of POAG from developing among a group of patients with OHTN). The NNT is calculated as 1/ARR, rounded to the next highest whole number.

For the OHTS, the NNT is 20 – that means one would have to treat 20 patients with OHTN to prevent one case of POAG from developing. A lower value for the NNT is desirable for any treatment intervention and an NNT in the range of 2–5 is generally regarded as indicative of an effective treatment (the NNT for the Early Manifest Glaucoma Trial where newly diagnosed OAG patients were randomized to treatment versus observation was 6),29 but a higher NNT may be acceptable for prophylactic treatments. The OHTS can be considered a prophylactic or preventive trial.

Interestingly, if the RRR stays constant, but the number of people reaching an endpoint increases, then the NNT goes down. A case in point regards the subset of African-Americans enrolled in the OHTS. The 5-year risk of converting from OHTN to POAG for African-Americans in the OHTS was 8.4% in the medical therapy arm and 16.1% in the observation arm.42 Thus, the ARR is 16.1–8.4 or 7.7% and the RRR is 8.4/16.1 or 48%. Overall, the NNT is 1/0.077 or 13. So among African-Americans, one would have to treat 13 patients with OHTN to prevent one case of POAG.

The ARR, RRR, and NNT provide quantitative insights into the results of RCTs yielding a global estimate of treatment effectiveness, but they do not tell us which

### Table 2.2 Randomized clinical trials assessing the effectiveness of medical therapy for exfoliation glaucoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Quality score</th>
<th>Outcome measured</th>
<th>Efficacy</th>
<th>Magnitude of effect</th>
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<tbody>
<tr>
<td>Konstas et al16</td>
<td>6</td>
<td>Diurnal IOP</td>
<td>Travatan&gt;Latanoprost</td>
<td>&lt;1.5 mmHg difference</td>
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<tr>
<td>Konstas et al17</td>
<td>5</td>
<td>Diurnal IOP</td>
<td>Bimatoprost&gt;Latanoprost&lt;1.5 mmHg difference</td>
<td></td>
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<tr>
<td>Parmaksiz et al38</td>
<td>1</td>
<td>Diurnal IOP</td>
<td>Dorzolamide-Timolol fixed combination&gt;Travoprost&gt;Latanoprost</td>
<td>&lt;1.5 mmHg difference</td>
</tr>
<tr>
<td>Konstas et al39</td>
<td>5</td>
<td>Diurnal IOP</td>
<td>Latanoprost&gt;Timolol</td>
<td>&gt;1.5 mmHg difference</td>
</tr>
<tr>
<td>Konstas et al40</td>
<td>4</td>
<td>10 AM IOP</td>
<td>Dorzolamide-Timolol fixed combination&gt;Latanoprost</td>
<td>No</td>
</tr>
</tbody>
</table>

*Favors industry-sponsored product*
individual patient requires treatment. The reader should be cautioned from concluding that all African-Americans with OHTN should be treated because the NNT is 13 when compared with an NNT of 20 overall. The decision to treat individual OHTN patients is better guided by the glaucoma risk calculator. The calculator, which has been validated in patients outside the OHTS accounts for important risk factors that predict conversion from OHTN to POAG and provides a 5-year risk estimate of converting from OHTN to POAG. The parameters that go into the calculation are age, mean IOP, central corneal thickness, vertical cup-disc ratio, and mean defect on the Humphrey visual field. Race is not entered into the calculator because multivariable analysis indicated that race was not an independent risk factor for conversion from OHTN to POAG. So a 48-year-old patient with mean IOP of 24 mmHg, OU; CCT of 520 µm OU; CDR = 0.4 OU; and PSD of 1.5 dB OD and 1.7 dB OS has a 5-year risk of converting to POAG of 15%. If one uses the calculator to stratify patients into low (≤5% in 5 years), medium (5–15% risk in 5 years) or high (>15% risk in 5 years) risk of converting to POAG, then this person, regardless of race, would have a moderate-to-high increased risk of converting to POAG. As it turns out, African-Americans will tend to fall into the high-risk category by virtue of the fact that they tend to have thinner corneas than their Caucasian counterparts. Nonetheless, an African-American subject with thick corneas does not necessarily have to go on treatment because the NNT for African-Americans overall is 13. Ultimately, the risk calculator should not be viewed as the instrument that rigidly guides treatment decisions, as that is an individual decision between the patient and doctor.

All treatment interventions have side effects relative to observation without therapy or an alternative treatment. Thus, it is useful to place an adverse effect profile in quantitative perspective as well when considering treatment for the individual patient. The term number needed to harm (NNH) is the number of patients that need to be treated to harm one patient. In the Collaborative Initial Glaucoma Treatment Study (CIGTS), patients with newly diagnosed OAG were randomized to treatment with medical therapy or surgery to lower IOP. Both treatments were equally effective in stabilizing vision and the visual field over a 5-year period. In fact, both treatments seem to have equivalent impact on quality-of-life measures. Nevertheless, 9% of patients in the medical therapy arm developed cataracts requiring surgical intervention, while 20% of patients in the surgical arm required cataract extraction. Thus, the NNH is calculated as 1/0.2–0.09 or 9. Thus in treating nine newly diagnosed patients with surgery first, the clinician would induce one extra cataract requiring surgical removal. A low NNH is not desirable, especially when the treatment inducing harm is not better than the alternative therapy (in this case medicine first). With that said, the “harm” in this case was a cataract that produces vision loss that is reversible with cataract extraction. In fact, CIGTS researchers show that cataract surgery in patients with prior filtration surgery is quite successful.

While the NNT and NNH provide quantitative interpretation of RCT results in terms of how they benefit patients, they do not tell us if treatment is cost-effective. Cost-effectiveness is a somewhat controversial term because it indicates there is a cost above which society cannot bear the burden of treating a specific condition. We like to think that ideally we should spare no cost in preventing glaucoma, but in reality, resources are limited and must be distributed judiciously such that the most treatable conditions are addressed on a societal level. Certainly, we would not want to spend so much money on treating OHTN that there are no resources available to care for patients with cataract or progressive POAG. The costs of healthcare have risen by about 20% per year from 1998 to 2004, and society needs to allocate finite resources for the most cost-effective treatments. The National Institute for Clinical Excellence has set a ceiling for annual costs associated with treating any disease, which reflects the resources available in an affluent country. Basically, if the incremental cost-effectiveness ratio (ICER) is greater than a societal cutoff for willingness to pay, the treatment is regarded as not cost-effective. The upper limit for ICER may be much lower in countries of more limited means. The ICER is calculated using RCT data, the actual costs of treating or observing the condition in question, and accounting for the number of years of life people would be willing to swap in order to remain free of the condition in question. The ICER for treating all OHTN patients is approximately $89,000. That means the incremental cost of treating all OHTN patients to prevent one case of POAG is $89,000, a value that is of borderline cost-effectiveness even for a highly developed country like the United States. If we limit treatment, for example, to those patients with CCT 40 µm below the norm (550 µm), then the ICER is close to $37,000. Similarly, it is cost-effective to treat OHTN patients over the age of 76 (two decades above the age of 56), IOP >29 mmHg (4 mmHg above the IOP of 25 mmHg), and with vertical CDR of 0.6 or more (0.2 units above 0.4) because in each case the ICER is less than $50,000.

2.3.6 What Do We Do When There Is Little or no Evidence?

You are a busy glaucoma specialist and you are emotionally shaken because in the past 2 months you have performed two combined cataract extractions with trabeculectomy procedures that resulted in suprachoroidal hemorrhage – one occurred intraoperatively and one occurred postoperatively.
In both instances, the patients developed excruciating pain, and in one instance, the vision went to light perception (LP) and did not improve. You are trying to decide whether there are preoperative measures to consider to prevent this from ever happening to you again. The experience has been devastating for the patients and for you. Your question is quite simple: What can be done to prevent suprachoroidal hemorrhage from developing? Very quickly you discover that there are no trials designed to answer this question. In fact, it is likely that there will never be a trial to answer this question because suprachoroidal hemorrhage is a relatively rare event and a trial would have to include a large number of patients in order to be adequately powered to determine if a particular intervention reduced the rate of suprachoroidal hemorrhage. While suprachoroidal hemorrhage is rare, it seems like a common event when it happens to one of your patients. So you hope to find some evidence that can help you. In this instance, the best source of evidence that can provide the answer to your question is observational studies. Observational studies may point to risk factors for the development of suprachoroidal hemorrhages. Those risk factors may lead you to adopt some strategies to minimize the development of suprachoroidal hemorrhage.

The source of bleeding in suprachoroidal hemorrhages is the posterior ciliary arteries that bridge the sclera and enter the choroidal tissue. The literature review indicates that the risk factors for suprachoroidal hemorrhage can be divided into systemic and ocular risk factors. Systemic risk factors include older age, hypertension, atherosclerosis, and intraoperative tachycardia. The insight that you gain from this list is that you hope to find some evidence that can help you. In this instance, the best source of evidence that can provide the answer to your question is observational studies. Observational studies may point to risk factors for the development of suprachoroidal hemorrhages. Those risk factors may lead you to adopt some strategies to minimize the development of suprachoroidal hemorrhage.

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2.4 Conclusion

One of the wonderful things about the study of medicine is that the learning process continues for a lifetime. Adhering to EBM is like maintaining your continuing medical education. Physicians will benefit from engaging in the EBM process throughout their career. It allows one to track emerging practice trends (such as the intraocular injection of anti-angiogenic agents in the management of neovascular glaucoma) and make rational decisions about adopting new management schema. One shortcoming is bringing EBM to the exam lane. The EBM process is not an exercise that can be performed when the patient is in our exam chair; however, once we have gone through the EBM process, it will certainly be absorbed into our practice patterns and help the next patients who present with similar problems. Furthermore, most of the searches for evidence are manual ones because ophthalmic meta-analytic topic reviews are just beginning to appear in the Cochrane database. At the current time, many glaucoma management issues cannot be resolved with the EBM process. The emergence of the electronic medical record, which requires a computer hooked up to the Internet in every exam lane, certainly helps us perform real-time calculations of risk for developing POAG in OHTN patients. In the end, the EBM process is about delivering the very best care for our patients.

Clinical Pearls

- EBM is a process whereby the best medical evidence in the literature is applied to patients with specific clinical problems.
- The EBM process involves four steps: (1) formulation of a clinical question, (2) assembly of the evidence that addresses that question, (3) an assessment of the quality of available evidence, and (4) application of the evidence to a particular patient.
- The absolute risk reduction, relative risk reduction, and number needed to treat represent quantitative measures to assess efficacy of an intervention in a RCT. The number needed to harm represents a quantitative measure to assess the adverse effects of an intervention in a randomized clinical trial.
- Most clinical challenges in glaucoma do not have a directly applicable randomized trial that addresses the problem.
References

21. Konstas AG, Mylopoulos N, Karabatsas CH, et al. Diurnal intraocular pressure reduction with latanoprost 0.005% compared to timolol maleate 0.5% as monotherapy in subjects with exfoliation glaucoma. Eye 2004;18:893–899


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