Letters

A Measure of Comparative Intraocular Pressure: The Glaucoma Burden Index

There is ever-intensifying interest in new glaucoma interventions, from less invasive glaucoma surgeries to alternative drug delivery systems. In assessing the efficacy of these interventions, invariably the primary outcome measure is centered on intraocular pressure (IOP), as IOP is the only modifiable risk factor for glaucoma.

Study confounders. The focus on IOP as an endpoint for studies is not without limitations. One major confounding factor is the concomitant use of medication at the time of patient enrollment and for the duration of data collection. New medications might be introduced after a specific intervention, and existing medications are sometimes tapered and stopped during the study period.

These events can confound proper evaluation of the treatment effect, and there are no agreed-upon methods to account for this, other than burdensome washout events at the start or end of a study or specifically prescribed treatment events that may not be practical during the time that the study is being conducted. Washout IOPs are also time-consuming and costly in real-world studies and are often not supported by institutional review boards due to the possibility of a participant incurring an injury to the optic nerve during periods of nontreatment.

These issues are magnified for retrospective studies in which real-world data are interpreted with inability to account for the medication effect as a whole. In addition, it may be of value to compare studies retrospectively and tease out details on how one treatment might compare to another treatment. Leveling the playing field regarding each study's use of medications would be valuable in these circumstances.

Index of IOP. If we were to combine IOP and medication use into a single measure, we might be able to eliminate a major confounding factor and provide a more objective comparison between study populations in different studies. This idea that we are proposing could be thought of as an index of comparative IOP.

In many respects, this index could represent glaucoma burden. One could state that the higher the IOP, the greater the "glaucoma burden" on any given optic nerve. Similarly, one could postulate that the greater the number of medications needed to achieve said IOP, the greater the glaucoma burden.

We are fortunate in that Jampel et al. have provided blueprints for such an index of comparative IOP.[1] Using IOP washout data from a prospective trial, they determined the effectiveness of one, two, and three glaucoma medications. When one medication was washed out, the IOP rose 5.4 mm Hg; two medications, 6.9 mm Hg; and three medications, 9.0 mm Hg.

One study examined the effect of adding a fourth medication and found that it resulted in a 3.5 mm Hg drop in IOP at 12 months.[2] However, the period studied was January through December 2000, and the most frequently added medication was a prostaglandin analog. This does not reflect current practice patterns for which a prostaglandin analog is considered first-line therapy and would rarely be the fourth agent added to a patient's regimen. We chose 1.5 mm Hg as the postulated effect of the addition of a fourth glaucoma medication. While this is somewhat arbitrary, it does reflect the authors' clinical impression of the effectiveness of a fourth glaucoma medication.

Thus, the algorithm we propose for the glaucoma burden index (GBI) is as follows:

- If number of medications is zero, GBI = IOP
- If number of medications is 1, GBI = IOP + 5.4
- If number of medications is 2, GBI = IOP + 6.9
- If number of medications is 3, GBI = IOP + 9.0
- If number of medications is 4, GBI = IOP +10.5

The literature is clear that lowering IOP slows glaucoma progression.[3] We are not proposing replacing IOP as a measure of disease risk in an individual patient. Rather, the GBI would allow assessment of comparative IOP across populations as well as objective comparisons of interventions in different clinical trials.

TABLE 1: Relationship between IOP, medication use, and glaucoma burden

IOP	Meds	GBI
15	1	20.4
15	2	21.9
15	3	24.0
15	4	25.5

As a more objective method of differentiating between new medical and surgical interventions, the GBI can help researchers, clinicians, and industry members alike. The hope would be that we would have a new tool to better guide our current understanding of available therapies as well as enhance our ability to categorize the therapeutic effects of future interventions.

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1 Jampel HD et al. *JAMA Ophthalmol.* 2014;132(4):390-395.
2 Neelakantan A et al. *J Glaucoma.* 2004;13(2):130-136.
3 Heijl A et al. *Arch Ophthalmol.* 2002;120(10):1268-1279.

A Response

"A Measure of Comparative Intraocular Pressure: The Glaucoma Burden Index" keenly sheds light on some of the challenges in comparing studies performed without rigorous medication washouts at baseline and last follow-up. The authors' proposed solution, a glaucoma burden index (GBI), is an interesting concept and could prove valuable in assessing the burden of medications on patients' quality of life and assessing costs related to glaucoma treatment.

While the authors' criticisms of randomized clinical trials (RCTs) do have some merit, they do not consider the fact that many seminal glaucoma RCTs in the last few decades have accounted for inclusion/exclusion criteria relatively well, and some have looked at optic nerve status or even visual fields rather than IOP alone as determinants.

In the table that the authors have proposed, an increased number of medications is associated with increased GBI. Despite the letter's attention to the confounding effects of medications on IOP, this design fails to account for the real impact on patients—in particular, further damage to the optic nerve and disease progression.

The index also fails to account for issues such as patient forgetfulness, improper eyedrop administration, and financial barriers, all of which have the potential to affect patient responses to medications (and incremental washout) in variable ways that yet unfortunately cannot be accurately measured. Furthermore, medications vary in efficacy, dosing frequency, and side effects, which is why the FDA and the American Glaucoma Society recently concluded that medication washouts should be performed at baseline and last follow-up, which is the current standard for new devices.[1]

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1 www.fda.gov/downloads/MedicalDevices/NewsEvents/.../UCM390327.pdf.

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