

FROM THE TRENCHES

What is maximal medical therapy today? Three physicians share their thoughts.

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The dynamic of medical treatment for glaucoma and the concept of maximal medical treatment have undergone a dramatic metamorphosis during the past decade. Notwithstanding the appeal and safety of laser trabeculoplasty, the vast majority of patients are introduced to glaucoma treatment using medication. Today's emphasis is

on target-driven therapy and tolerability.

TARGET-DRIVEN THERAPY

This concept stems from the belief that a target IOP and the consistency of maintaining that goal direct glaucoma management. Multiple randomized controlled trials have supported and reinforced the construct—the Advanced Glaucoma Intervention Study (AGIS), Early Manifest Glaucoma Trial (EMGT), Ocular Hypertension Treatment Study (OHTS), Collaborative Initial Glaucoma Treatment Study (CIGTS), and Collaborative Normal Tension Glaucoma Study (CNTGS).¹⁻⁷

Target-driven therapy also focuses on a complementary mechanism of action when adding an agent or switching from one medication to another. For example, a patient using a prostaglandin analogue (PGA) whose IOP control is good but not optimal would benefit from a drug that has a different mechanism of pharmacological action such as one that inhibits aqueous production or enhances trabecular meshwork outflow. In contrast, a patient who does not respond to a PGA is unlikely to fare better with a different PGA within the same class.

TOLERABILITY

Traditionally, tolerability is assessed based on the side effects of medical treatment. Fortunately, it is relatively straightforward for patients and clinicians to link untoward complications to a medication.

Newer factors in the tolerability “bucket” are cost and availability. The growing influence of insurance companies on the selection of medications has been associated with the emergence of a new intermediary referred to as a *pharmacy benefit manager*. Accompanying the rise of this third-party “broker” is the cost-benefit generic package. Sometimes, the use of generic agents makes good sense and good medicine. Sometimes, it does not make any sense at all. For example, why does the quintessential generic drug pilocarpine often cost more than latanoprost or timolol? Compounding the

complexity of medical treatment for patients are the copay and limitations of volume to a 30-day supply.

Clinicians face challenges in this area as well. Phone calls and faxed requests for changes in a patient's medication now tend to be the rule rather than the exception. When a more expensive drug is indicated, eye care providers must engage in a straightforward but cumbersome process to bypass the change to a cheaper agent referred to as a *prior authorization request*.

MAXIMAL MEDICAL THERAPY

Maximal medical treatment has evolved from requiring a patient to use or be exposed to all five classes of medication to a focus on the maximal number of medications required to reach the target IOP at minimal cost and optimal tolerability. Neelakantan and colleagues pointed out that the likelihood of patients' consistently using more than two topical drugs is less than 10% when measured over a year.⁸ The take-home point is that either the vast majority of patients will not refill the prescription for a third or fourth drug or that those additional medications are unlikely to be efficacious.

Maximal medical treatment is patient directed. It has changed from the number of medications to the number of bottles. It encompasses ease of use and out-of-pocket expenses. For most patients, “targeted” medical therapy is one bottle used once a day. For others, targeted therapy requires two bottles, one used once and the other twice a day. Rarely will additional medications be needed or successful in the long run.

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Because glaucoma is a chronic condition, medical treatment is frequently a first-line and long-term endeavor for both the prescribing physician and the patient. Once a decision is made to pursue IOP-lowering therapy, a variety of medication classes and combinations of medications from which to choose is available.

THEN AND NOW

The term *maximal medical therapy* has had different meanings over the years. Before the introduction of the topical β -blockers in the 1970s, cholinergic agents (pilocarpine), adrenergic agents (epinephrine/dipivefrin), and oral carbonic anhydrase inhibitors were the mainstay of glaucoma medical regimens. Frequent dosing and poor tolerance of local and systemic side effects were the norm. Because there were no other low-risk alternatives (eg, laser trabeculoplasty), however, physicians and patients were limited to this treatment.

Today, several classes of medication are available, including prostaglandin analogues, topical carbonic anhydrase inhibitors, α -2 adrenergic agonist agents, fixed-combination drugs, and preservative-free alternatives. Has this bounty changed the definition of maximal medical therapy? The answer depends on whether the definition is based on how many drops a physician can prescribe or—my preference—a careful evaluation of each agent's efficacy, cost, and side effect profile and the patient's adherence to therapy.

EFFICACY

I always tell patients, "If the drug is not lowering your pressure, then I will not continue prescribing it." This statement sounds simple and obvious, but there are many patients on a myriad of medications that were not assessed as individual drugs when added to their regimen. Fixed-combination medications represent excellent alternatives for many individuals, but if a patient is to use a drug product long term, my guidelines are to establish its efficacy at lowering IOP by a minimum of 15% to 20%, given diurnal fluctuations over time. The addition of a third or fourth medication to a regimen often does not provide significant additive IOP lowering but frequently results in decreased adherence.

COST

Since implementation of Medicare part D prescription drug benefits, cost-related nonadherence to prescribed glaucoma therapy has remained a problem.¹ Because the cost and accessibility of both brand-name and generic medications fluctuate under the current system of insurance payers and pharmacy benefit plans, physicians may be required

to change a patient's prescriptions periodically in order to control his or her out-of-pocket costs. These transitions can alter side effects, tolerability, and efficacy of the drugs.^{2,3}

SIDE EFFECT PROFILE

Discussions with patients about the most common local and systemic effects of topical therapy are important. The identification of allergic reactions and intolerance should lead to discontinuation of a drug (Figure). That said, some patients are reluctant to stop a medication, because doing so may prompt recommendations for alternative and potentially more invasive treatment, whereas other patients are not aware that the ocular or periocular irritation they are experiencing is related to their topical medication. This problem can be much more serious (eg, bronchospasm and bradycardia). I have personally cared for patients whose scheduled placement of a pacemaker was cancelled after the discontinuation of a topical β -blocker!

Growing awareness of ocular surface toxicity to preservatives⁴ such as benzalkonium chloride has led to the availability of preservative-free and alternatively preserved therapies, which have allowed many patients to continue topical glaucoma therapy.⁵

ADHERENCE

Multiple studies have shown that clinicians cannot determine which patients are taking medications based on their own reporting, educational or socioeconomic status, etc.⁶ What is certain is that a large percentage of patients are using medication incorrectly or not at all. The number of doses and medications may be inversely proportional to the level of adherence to therapeutic regimens, but even once-daily medications do not guarantee that the agents will be used as prescribed.⁷

Few major clinical trials in glaucoma have focused on patients' quality of life.⁸ Practicing physicians have a responsibility to discuss with patients not only the stability



Figure. Allergic reaction to topical therapy.

or progression of their disease but also how well they are tolerating therapy according to the criteria mentioned earlier. Such conversations may indicate whether or not zero to nine drops per day are acceptable and efficacious. When patients do not tolerate topical medical therapy resulting in IOP lowering to the target range, then a discussion of alternatives is required.

Physicians are fortunate to have additional options to offer to patients, including laser trabeculoplasty, microinvasive glaucoma surgeries, and more traditional incisional alternatives. The key, of course, is always to weigh the risks and benefits for each individual patient.

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Glaucoma may be divided into various subsets, and each patient is an individual. For these reasons, the treatment of each patient varies.

SIDE EFFECTS

Maximal medical therapy refers to the most a patient can tolerate. Today, patients and their physicians are lucky to have five categories of topical medications from which to choose: β -blockers, carbonic anhydrase inhibitors, α -agonists, prostaglandin analogues (PGAs), and cholinergics (eg, pilocarpine). There are also oral glaucoma medications (acetazolamide and methazolamide). Unfortunately, all medications carry side effects—systemic,^{1,2} neuropsychiatric,³⁻⁸ and cardiovascular (myocardial infarction).⁹ One drop of timolol 0.5% significantly decreases pulse rate and exercise tolerance.^{10,11} Although rare, brimonidine can induce psychosis.¹² Carbonic anhydrase inhibitors can decrease libido, a side effect most likely attributable to malaise and depression.¹³

I advise my patients to use the techniques of eyelid closure and nasolacrimal duct obstruction when administering topical ophthalmic medications. Both help reduce adverse systemic side effects and increase the local effects on the eye.^{14,15}

When prescribing topical β -blockers, it is important to consider patients' other systemic medications. The latter's effects can be compounded in patients taking topical β -blockers.¹⁶ Those on antipsychotics (thioridazine or chlorpromazine for schizophrenia) can develop increased serum levels of the drugs when taking topical ophthalmic β -blockers,¹⁷⁻¹⁹ possibly because of competition in the liver where these drugs are metabolized.

LIFESTYLE

Patients may not want to use topical glaucoma drops for a variety of reasons. For example, those who wear contact lenses may find the frequent instillation of medication particularly inconvenient. For these individuals, once-daily dosing (PGAs or a once-daily β -blocker) may be the least onerous choice. Other patients physically cannot instill eye drops and may be better served by laser therapy such as selective laser trabeculoplasty (SLT). Patients who work full time may not be able to administer drops in the middle of the day. For others, the cost of medication may be a barrier.

COMORBIDITIES

Comorbidities such as asthma, coronary artery disease, hypotension, bradycardia, and renal failure can preclude medical glaucoma therapy. A patient may be sensitive to the side effects of certain medications. For example, acetazolamide has been reported to cause a host of side effects, including hypokalemia, fatigue, dehydration, constipation, diarrhea, paresthesias, and renal stones. Although well tolerated, PGAs can cause hypertrichosis. In my experience, most heterosexual male patients do not want long eyelashes and therefore request a different medication. Another known side effect of PGAs is orbital fat atrophy with resultant enophthalmos. Some patients may tolerate this cosmetic change, whereas others say it makes them look sickly.

MY APPROACH

After patients complete a 1-month trial of a medication, I will reassess them to ensure that they are responding to and can tolerate treatment. If they tell me that instilling the drop is difficult, I will offer SLT.

Dry eye disease is a common ophthalmologic condition. Many topical glaucoma medications contain the preservative benzalkonium chloride, which is known to contribute

to dry eye disease by causing inflammation and cellular damage. If one of my patients requires more than one topical drop, I will consider preservative-free options, although preauthorization paperwork is required.

When patients present to my office after having undergone one or more glaucoma surgeries, I explain that the procedures may not suffice to achieve their target IOP. In such cases, I note that supplemental treatment can consist of topical glaucoma medications or SLT. If a patient has a history of trabeculectomy or the placement of a glaucoma drainage device and cannot tolerate medical or laser treatment, a revision of the earlier procedure may be an option. In the case of a prior trabeculectomy, a needling procedure ab externo can be performed in lieu of adding medications.

CONCLUSION

The tolerability of medical therapy depends on the patient. Treatment must be tailored to his or her lifestyle, financial situation, comorbidities, and ability to tolerate side effects. Patients always have options, and it is my job to educate them and to help them make an informed decision on their medical care. ■

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