Journal of Clinical & Experimental Ophthalmology

Schwartz et al., J Clin Exp Ophthalmol 2012, 3:8
DOI: 10.4172/2155-9570.1000248

Research Article Open Access

Adherence and Persistence with Glaucoma Therapy: Brimonidine/Timolol versus Dorzolamide/Timolol and Various Two-Bottle Combinations

Gail F. Schwartz[1,2]*, Caroline Burk[3], Teresa Bennett[4] and Vaishali D. Patel[5]

[1]*Greater Baltimore Medical Center, Baltimore, MD, USA*
[2]*Wilmer Eye Institute, Johns Hopkins University, Baltimore, MD, USA*
[3]*Health Outcomes Consultant, Laguna Beach, CA, USA*
[4]*Source Healthcare Analytics, Phoenix, AZ, USA*
[5]*Allergan, Inc., Irvine, CA, USA*

Abstract

Purpose: Patients with glaucoma often require multiple topical medications to reach target intraocular pressure. This database analysis examined persistence and adherence in patients' prescribed fixed-combination brimonidine/timolol, fixed-combination dorzolamide/timolol, or various commonly used two-bottle combinations.

Participants: Glaucoma patients (ICD-9 code: 365.xx; n=7883) from the Source Healthcare Analytics Source® Lx database with an index prescription for fixed-combination brimonidine/timolol, fixed-combination dorzolamide/timolol, or various commonly used two-bottle combinations during the 6-month qualifying period (January 2008–June 2008), but not the 12 months before, were included.

Methods: In this retrospective prescription database analysis, adherence and persistence for fixed-combination brimonidine/timolol were compared to fixed-combination dorzolamide/timolol and various commonly used two-bottle combinations. The two-bottle arms were: β-blocker+brimonidine; β-blocker+carbonic anhydrase inhibitor; β-blocker+prostaglandin analogue; carbonic anhydrase inhibitor+brimonidine; carbonic anhydrase inhibitor+prostaglandin analogue; and prostaglandin analogue+brimonidine.

Main outcome measures: Persistence for brimonidine/timolol was compared with each of the comparators using Kaplan-Meier survival analysis for 12 months after the index prescription. Adherence was assessed using the medication possession ratio.

Results: Kaplan-Meier analyses found that a significantly greater proportion of patients remained on treatment with brimonidine/timolol (34.9%) compared with each of the other treatments (13.4%–20.8%; $p<0.0001$) at the end of the study period. In addition, the 12-month medication possession ratio was significantly higher for brimonidine/timolol (42.7%) than for each of the two-bottle arms (23.3%–34.9%; $p<0.0001$ for all comparisons). The medication possession ratio for brimonidine/timolol was also slightly, but significantly, higher than that for dorzolamide/timolol (40.6%; $p=0.0208$).

Conclusions: Persistence and adherence are higher with a fixed-combination single bottle of brimonidine/timolol than with fixed-combination dorzolamide/timolol and commonly used two-bottle combinations.

Keywords: Adherence; Brimonidine/timolol; Combination therapy; Dorzolamide/timolol; Glaucoma; Persistence

Introduction

Glaucoma is among the leading causes of irreversible blindness in the United States and worldwide [1,2]. The prevalence of open-angle glaucoma, the most common form of glaucoma, in the population aged ≥ 40 years in the United States has been estimated at 1.86%, with an estimated 2.22 million people in the United States affected in 2000, and the total expected to increase to 3.36 million in 2020 due to the aging population [3]. Glaucoma is characterized by optic neuropathy that is derived from various risk factors, including increased intraocular pressure (IOP) [2,4], which is an important risk factor because it is modifiable [5]. Glaucoma progression (both structural and functional) is associated with elevated IOP, and lowering IOP has been shown in a number of studies to inhibit the progression of glaucomatous optic nerve damage [6-9], leading to a therapeutic focus on lowering IOP.

IOP can be lowered by pharmacological therapy, laser therapy, or incisional surgery (alone or in combination) [10]. Topical medications are an effective initial therapy in many patients [10], but studies have shown that it is often necessary to use multiple topical medications to achieve target IOP [7,9,11]. For patients in whom treatment with multiple topical medications is required, this may be achieved by administering each medication separately from different bottles, or by using a fixed-combination product that combines medications in a single bottle. The reduction in IOP achieved with a fixed combination of two agents is greater than that with either agent alone, and is at least equal to that with the two components administered from separate bottles [12-14]. Fixed-combination products have the potential to further facilitate IOP reduction. Such products combine two medications with combined or complementary actions on IOP.

***Corresponding author:** Gail F. Schwartz, MD, GBMC Physicians Pavilion East, 6565 N. Charles St, Suite 302, Baltimore, MD 21204, USA, Tel: (410) 825-9225; Fax: (410) 825-9229; E-mail: schwartzgf@aol.com

Received August 16, 2012; **Accepted** October 10, 2012; **Published** October 17, 2012

Citation: Schwartz GF, Burk C, Bennett T, Patel VD (2012) Adherence and Persistence with Glaucoma Therapy: Brimonidine/Timolol versus Dorzolamide/Timolol and Various Two-Bottle Combinations. J Clin Exp Ophthalmol 3:248. doi:10.4172/2155-9570.1000248

In addition, they may reduce "washout" effects that may occur with sequential administration of two separate topical medications (where the first medication may be washed away by the second), and may encourage better patient adherence and persistence with treatment [15].

As in any condition, persistence (ie, continuity of the regimen over time) and adherence (ie, the accuracy with which a patient follows the prescribed regimen) to therapy is essential for adequately treating glaucoma. Poor adherence and persistence with glaucoma medication may lead to worse clinical outcomes [16]. However, the necessary level of adherence is frequently not achieved by patients with glaucoma [17]. One of the factors shown to be associated with lower rates of persistence and adherence is use of multiple glaucoma medications, particularly when administered in separate bottles [18-22]. Thus, use of fixed combinations of multiple topical glaucoma medications may help to improve persistence and adherence; studies examining persistence with fixed-combination medications support this hypothesis [20,23].

The purpose of this analysis was to examine whether persistence and adherence differ between patients prescribed a fixed combination of topical brimonidine/timolol as a single bottle versus those prescribed fixed-combination dorzolamide/timolol, or various two-bottle combinations.

Materials and Methods

This analysis utilized data from the Source Healthcare Analytics Source® Lx database. Source® Lx is a longitudinal patient-level database of submitted prescription, physician practice (CMS1500), and hospital (CMS1450) administrative claims for over 115 million patients, captured as they move between the provider and the payer. The Source® Lx database is a patient-level, integrated data source with broad and representative geographic coverage, which includes a unique patient-linking process that provides a more complete view of patient treatment history, and enables patients to be tracked even if they change insurance plans. The database is representative of the census population across age, sex, and geography [24], and includes patients from a wide representation of plans. Qualifying sample patients from the database were tracked over time. The analysis was compliant with the Health Insurance Portability and Accountability Act (HIPAA). Institutional review board approval was not required because the data were collected on a secondary, anonymous basis.

Patients with a diagnosis of glaucoma (ICD-9 code: 365.xx) who had an index (qualifying) prescription for a product of interest during the 6-month qualifying period from January 2008 to June 2008, and no prescription for the same product during the 12 months prior to the index prescription (ie, product naïve), were identified. To qualify for the two-bottle combination arms, patients were required to have a prescription for an additional glaucoma drug within 30 days of the index drug. Furthermore, patients had to be product naïve (no drug within the 12-month pre-index period) for at least one of those two drugs. The fixed-combination arms were brimonidine/timolol (reference group) and dorzolamide/timolol. The two-bottle combination arms were: β-blocker+brimonidine; β-blocker+carbonic anhydrase inhibitor (CAI; acetazolamide, methazolamide, brinzolamide, or dorzolamide); β-blocker+prostaglandin analogue (PGA; bimatoprost, latanoprost, or travoprost); CAI+brimonidine; CAI+PGA; and PGA+brimonidine.

The days' supply for each medication was calculated using the following formula:

Days' supply=[number of drops/bottle]÷([number of drops/dose]×[number of administrations/day]).

Data for the number of drops per bottle was obtained from previously published sources [25,26].

Bilateral use of eye drops was assumed for all patients. Administration of medication per labeling was used for all medications. This method was used to calculate a more accurate days' supply because the day's supply field available in claims databases is subject to inaccuracy for non-discrete drug formulations such as eye drops [27,28].

Statistical Methods

Medication persistence

Kaplan-Meier analysis was performed to compare the proportion of patients remaining on therapy, at each month for up to 12 months past the index prescription, between fixed-combination brimonidine/timolol and the comparators. A patient was deemed to be "on continuous therapy" as long as they continued to refill the prescription(s) before the days' supply plus the grace period (60 days) applicable to the previous fill ran out. If a patient did not refill the next prescription within this time period, they were deemed to be "off therapy." To determine the discontinuation date, the number of days' supply from the last prescription fill plus the 60-day grace period was considered. For the two-bottle combination cohorts, a similar methodology was applied. A patient was considered "off therapy" if they failed to refill either one of the two bottles within the required time period. It should be noted that this 60-day grace period is commonly used in other claims database studies in the literature [29-34]. P values were obtained using the log-rank test for homogeneity in the SAS/STAT software, version 9 for Windows (SAS Institute Inc., Cary, NC, USA) LIFETEST Procedure.

If a patient switched within the same class of medications (eg, from the PGA latanoprost to the PGA travoprost), the patient was not considered persistent on the index drug.

Medication adherence

Medication possession ratio (MPR) for fixed-combination brimonidine/timolol and dorzolamide/timolol was calculated using the following equation:

MPR=([number of days medication was "on hand"]÷365)×100.

For the two-bottle combination arms, MPR was calculated using the following equation:

MPR=([number of days both medications were "on hand"]÷365)×100.

Qualified patients for the analysis were tracked for 12 months after their index prescription to determine MPR. P values were based on a statistical test for comparing two binomial proportions using a normal approximation.

Proportion of patients on therapy by month after accounting for restarts

A descriptive analysis was conducted to assess difference in the proportion of patients remaining on therapy at each month for up to 12 months past the index prescription using the inclusion of restarts methodology from Schwartz et al. [35]. Discontinuation of therapy was defined as no refill of the study drug within the expiration period (number of days' supply from the last prescription fill plus a 60-day grace period). Among discontinued patients, restarts were defined as patients who refilled their index drug at any time after the expiration period. For the combination cohorts, a similar methodology was

applied. Discontinuation of therapies was defined as when at least one of the index drugs was not refilled within the expiration period. P values were based on a statistical test for comparing two binomial proportions using a normal approximation.

Results

The analysis included data from a total of 7883 patients: brimonidine/timolol (n=1242); dorzolamide/timolol (n=2868); β-blocker+brimonidine (n=365); β-blocker+CAI (n=236); β-blocker+PGA (n=1025); CAI+brimonidine (n=329); CAI+PGA (n=618); and PGA+brimonidine (n=1200). Differences among the groups in mean patient age were small (mean age, 69.7–71.9 years), although statistical significance versus brimonidine/timolol was reached in some groups (dorzolamide/timolol, β-blocker+PGA, CAI+PGA, and PGA+brimonidine; Table 1). Similarly, differences among groups in the proportion of female patients were small (proportion female, 52.5%–59.8%), although statistical significance versus brimonidine/timolol was reached in some groups (dorzolamide/timolol, β-blocker+CAI, β-blocker+PGA, and PGA+brimonidine; table 1).

Persistence with fixed-combination brimonidine/timolol compared with different agents using the Kaplan-Meier analysis over the 12-month period is shown in figure 1. The analysis showed that persistence was higher with fixed-combination brimonidine/timolol than with each of the comparators from month 6 onwards; a significantly greater proportion of patients remained on fixed-combination brimonidine/timolol (34.9%) compared with each of the comparator therapies (13.4%–20.8%; p<0.0001) at the end of the study period. The differences between fixed-combination brimonidine/timolol and the comparators remained significant (p<0.0001) in sensitivity analyses where the grace period was varied to 15, 30, or 90 days.

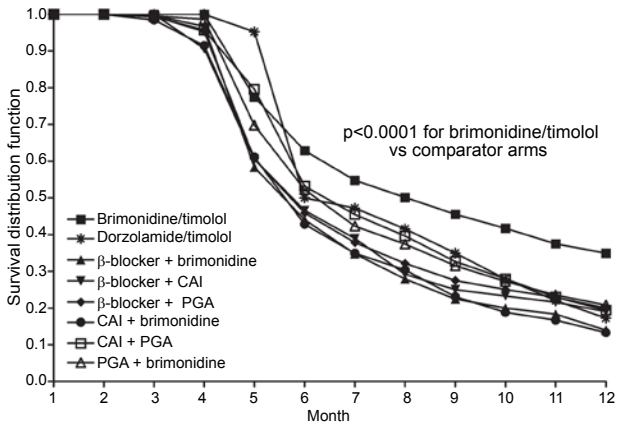
Adherence using MPRs over 12 months following the index prescription for fixed-combination brimonidine/timolol compared with each of the comparator therapies is shown in table 2. The MPR for fixed-combination brimonidine/timolol (42.7%) was significantly higher than the values for each of the two-bottle combination therapies, which ranged from 23.3% to 34.9% (p<0.0001 for all comparisons). The MPR for brimonidine/timolol was only slightly higher than that for fixed-combination dorzolamide/timolol (40.6%), although the difference reached statistical significance (p=0.0208).

The number of patients who restarted the index drug(s) during the evaluation period was 143 for brimonidine/timolol, 264 for dorzolamide/timolol, 29 for β-blocker+CAI, 183 for β-blocker+PGA, 32 for CAI+brimonidine, 73 for CAI+PGA, 194 for PGA+brimonidine, and 0 for β-blocker+brimonidine. The descriptive analysis looking

Treatment Arm	Mean Age, y	Sex, %		
		Female	Male	Unknown
Brimonidine/timolol (n=1242)	69.8	59.8	39.9	0.2
Dorzolamide/timolol (n=2868)	70.3**	56.3†	43.1	0.6
β-blocker+brimonidine (n=365)	70.0	57.8	41.4	0.8
β-blocker+CAI (n=236)	70.2	52.5*	46.6	0.8
β-blocker+PGA (n=1025)	71.9†	55.9*	44.0	0.1
CAI+brimonidine (n=329)	69.7	56.8	42.6	0.6
CAI+PGA (n=618)	70.3**	57.0	42.6	0.5
PGA+brimonidine (n=1200)	70.3†	56.6*	42.8	0.6

CAI: Carbonic Anhydrase Inhibitor; PGA: Prostaglandin Analogue
*p<0.05; **p<0.01; †p<0.0001 vs brimonidine/timolol

Table 1: Baseline demographics of patients with glaucoma included in analyses.



CAI: Carbonic Anhydrase Inhibitor; PGA: Prostaglandin Analogue

Figure 1: Kaplan-Meier analysis of patients with glaucoma remaining on a fixed combination of brimonidine/timolol compared with a fixed combination of dorzolamide/timolol or various two-bottle combinations of topical glaucoma therapy for up to 12 months following the index prescription.

Medication Combination	MPR, %	P Value vs Brimonidine/Timolol
Brimonidine/timolol (n=1242)	42.7	–
Dorzolamide/timolol (n=2868)	40.6	0.0208
β-blocker+brimonidine (n=365)	23.3	<0.0001
β-blocker+CAI (n=236)	25.0	<0.0001
β-blocker+PGA (n=1025)	25.4	<0.0001
CAI+brimonidine (n=329)	26.3	<0.0001
CAI+PGA (n=618)	34.9	<0.0001
PGA+brimonidine (n=1200)	32.2	<0.0001

CAI: Carbonic Anhydrase Inhibitor; MPR: Medication Possession Ratio; PGA: Prostaglandin Analogue

Table 2: MPRs for fixed-combination brimonidine/timolol versus fixed-combination dorzolamide/timolol or various two-bottle combinations of topical glaucoma therapy for up to 12 months following the index prescription.

at the proportion of patients on the index treatment at each month (allowing inclusion of restarts) showed that from month 5 onwards, with only a few exceptions, a significantly greater proportion of patients was on the fixed combination of brimonidine/timolol compared with each of the comparator groups (p<0.05; Table 3). Among patients with an index prescription for the fixed combination of brimonidine/timolol, 64% were on treatment at 6 months, and 45% at 12 months. In comparison, in the dorzolamide/timolol arm, 50% of patients were on treatment at 6 months and 24% at 12 months, while in the two-bottle arms, the proportion of patients on therapy ranged from 45%–55% at month 6, and 20%–33% at month 12. Similar significant differences between fixed-combination brimonidine/timolol and the two-bottle combinations were observed when the grace period was varied to 15, 30, or 90 days.

Discussion

Persistence and adherence with topical glaucoma medications is essential to maintain control of IOP and effectively treat glaucoma [36]. Our study evaluated both persistence (continuity of the regimen over time) and adherence (the accuracy with which a patient follows the prescribed regimen), as each of these parameters provides valuable information about whether a patient is taking their medication as their physician intends. The current analysis demonstrated that persistence with topical glaucoma therapy was higher with a fixed combination

Month	Brimonidine/ Timolol (n=1242)	Dorzolamide/ Timolol (n=2868)	β-blocker+Brimonidine (n=365)	β-blocker+CAI (n=236)	β-blocker+PGA (n=1025)	CAI+Brimonidine (n=329)	CAI+PGA (n=618)	PGA+Brimonidine (n=1200)
1	100	100	100	100	100	100	100	100
2	100	100	100	100	100	100	100	100
3	100	100	100	100	100	100	100	100
4	100	100	96.7	90.7†	95.7	92.4**	95.8	99.0
5	77.5	95.3‡	58.4‡	61.0‡	61.6‡	62.3‡	79.9	70.3*
6	64.1	50.2‡	45.8‡	49.2†	49.9‡	44.7‡	54.9**	53.6†
7	57.6	50.5**	38.9‡	42.8†	44.5‡	38.0‡	48.9**	46.3†
8	54.8	46.8**	36.2‡	33.9‡	40.8‡	35.0‡	44.5**	43.5†
9	52.3	42.0†	31.5‡	30.1‡	38.0‡	29.5‡	38.5‡	39.8‡
10	49.5	36.1‡	29.9‡	30.5‡	36.8‡	25.5‡	35.4‡	38.2†
11	46.5	30.3‡	28.8‡	28.8‡	34.3‡	23.4‡	30.7‡	35.4†
12	45.0	24.0‡	23.0‡	26.3‡	31.6‡	20.1‡	28.2‡	33.4†

CAI: Carbonic Anhydrase Inhibitor; PGA: Prostaglandin Analogue
*p<0.05; **p<0.01; †p<0.001; ‡p<0.0001 vs brimonidine/timolol

Table 3: Proportion of patients (%) with glaucoma on fixed-combination brimonidine/timolol versus fixed-combination dorzolamide/timolol or various two-bottle combinations of topical glaucoma therapy (with inclusion of restarts) each month for up to 12 months following the index prescription.

of brimonidine/timolol than with fixed-combination dorzolamide/timolol and various two-bottle combinations, as shown by both Kaplan-Meier survival analysis and an additional descriptive analysis of patients on therapy at each month that accounted for stopping and restarting of therapy. The MPR for fixed-combination brimonidine/timolol, a measure of adherence, was significantly higher than for each of the comparators over the study period. This higher adherence and persistence for fixed-combination brimonidine/timolol could be due to its superior tolerability compared with dorzolamide/timolol. However, claims databases do not have the necessary variables needed to test this hypothesis.

A study comparing persistence among patients with glaucoma receiving topical combination therapy administered via a single bottle (fixed combination of dorzolamide/timolol), a two-bottle combination (a β-blocker and one other glaucoma product), or a three-bottle combination (three different therapies) showed that persistence after 1 year was highest in those receiving the single-bottle therapy (35.3%), followed by the two-bottle combination (27.2%; p<0.0001 vs single-bottle therapy), with the three-bottle combination having the lowest persistence (23.9%; p<0.0001 vs single-bottle and two-bottle therapy) [20]. These findings are consistent with the results of the current study, showing that persistence was markedly higher with the single-bottle fixed combination of brimonidine/timolol than with various two-bottle combinations.

Caution must be used in making comparisons with persistence and adherence data from other analyses, as methodologies can differ between them. For example, the definitions used for persistence may differ, particularly with regard to how the days' supply is calculated and whether the analysis accounts for restarts following gaps in therapy, which is common in clinical practice and greatly influences the results of such analyses [35]. Studies may also use different grace periods within which patients are required to refill their prescription to be considered persistent. In the current study, with the primary analysis utilizing a 60-day grace period, a patient with only one or two prescriptions would still be considered "on therapy" for the duration that the grace period applied; thus, in the persistence analysis and the analysis of the proportion of patients on therapy by month (accounting for restarts), the proportion remains at 100% during the initial 3–4 months. Alternative grace periods were examined in a sensitivity analysis and showed similar findings to the primary analysis. Persistence began to decline across all products at approximately 5–6 months, although it remained higher with brimonidine/timolol; it is possible that this effect could have been associated with follow-up office visits and subsequent regimen changes, rather than patients lapsing from utilizing the prescribed treatment. Another factor that could have influenced the findings of the current study is that patients likely had to pay only one co-pay for prescriptions for fixed-combination brimonidine/timolol (although this may not be the case for all prescription plans), which could increase persistence. The findings could also have been influenced by demographic characteristics such as income; however, detailed patient demographics were not available in the database.

Similarly, using different definitions for adherence may lead to different findings for MPRs for glaucoma therapies. In the current analysis, the MPR with fixed-combination brimonidine/timolol (42.7%) was significantly higher than with each of the two-bottle combinations (23.3%–34.9%; p<0.0001). In addition, the MPR for brimonidine/timolol was slightly higher than with dorzolamide/timolol (40.6%), although the difference did reach statistical significance (p=0.0208). Given the small difference in MPR between the two fixed-combination arms, it should be considered whether this difference is clinically meaningful. Although the mean age of subjects in the brimonidine/timolol group was significantly lower than that of several of the two-bottle combination groups, it differed by only 2 years at most. Therefore, we do not expect these differences to affect our results. Other adherence analyses [37-39] report MPR results (depending upon the imputation method used for days' supply) ranging from 47% to 76.3%; thus, further studies evaluating the differences in persistence and adherence between fixed-combination brimonidine/timolol and dorzolamide/timolol are needed.

Physicians may not always be aware when a patient is not being adherent or persistent with glaucoma medication. Patients who are non-adherent or become non-persistent with glaucoma therapy commonly show cyclic behavior (eg, exhibiting good adherence during a short period preceding an office visit ["white coat adherence"], and subsequently declining in adherence over time following the visit, or restarting medication after periods of several months without use) [35,37]. If a patient has had a gap in therapy, but has resumed medication shortly before an office visit, the patient may appear to be at an optimal IOP, but may have had visual field progression as a result of the lapse in therapy [40]. In order to optimize patient adherence

and persistence with topical glaucoma therapy, it is important for physicians to recognize potential obstacles early in the treatment plan, and plan therapeutic interventions accordingly [41].

The nature of persistence behavior seen in patients with glaucoma is also an important consideration when conducting studies evaluating medication persistence, and it has been shown that it is important to account for restart rates [35]. In the current study, we conducted both a traditional Kaplan-Meier survival analysis and a secondary analysis of patients remaining on therapy that accounted for restarts. Both analyses were consistent in demonstrating significantly improved persistence between fixed-combination brimonidine/timolol and the comparator therapies.

There are some potential limitations of this study that should be considered when interpreting the findings. The analysis is based on prescription claims data; therefore, patients are not directly observed, and assumptions are made based on filling or apparent failure to fill prescriptions or refills. For example, if a patient did not fill their prescriptions for a period, but continued to use medication (eg, because of receiving medication samples), they may have been incorrectly categorized as being non-persistent or non-adherent to therapy. However, due to the extended 12-month time frame of follow-up, and the supplementary analysis accounting for restarts that would capture a patient filling the next prescription after finishing sample medication, this is less likely to have occurred or to have affected the findings of the study. In addition, since it is common for physicians to provide most patients with samples, we would expect the rate and impact of providing samples to be similar across the treatment arms, except perhaps for β-blockers, which may not have had samples available at the time of the study, Similarly, it cannot be determined why specific drugs were prescribed, or why a medication has been discontinued; physicians may switch a patient's medication due to noncompliance with a specific drug/combination, but also as a result of adverse effects. Another inherent limitation of claims data is that a patient filling the prescription is not a guarantee of them using the medication. In addition, by the design of this study, patients in the two-bottle combination cohort have a higher likelihood (probability) of failing to fill one of the medications than patients in the fixed-combination arms who are only getting one bottle. This may artificially show lower adherence in the two-bottle combination arms. However, if patients included in this study did inadvertently make such errors in requesting refills, this reflects the reality of how patients may make errors that impact their treatment, and further illustrates the potential benefit of a fixed-combination medication in reducing the risk of such errors leading to unintended alterations in the treatment received. It is difficult to know how comparable the group of patients included in our analysis is to the population of patients with glaucoma in the community; however, given that our sample was community-based and derived from a large, diverse dataset, we would expect the data to be representative of the population at large.

In conclusion, adherence and persistence with topical glaucoma therapy were higher with a fixed combination of brimonidine/timolol than with fixed-combination dorzolamide/timolol or various two-bottle combinations. Even with considering patient restart behavior, the fixed combination of brimonidine/timolol showed significantly higher persistence compared with other therapies. The results of this analysis illustrate the importance of understanding patient behavior as it relates to medication adherence and persistence, and that differences occur among glaucoma treatment patient populations.

Acknowledgements

Sushma Soni of inScience Communications, Springer Healthcare, provided editorial support, which was funded by Allergan, Inc. Tony Horn of Source Healthcare Analytics contributed to the data analysis and review of this manuscript.

Financial Support

The sponsor of this study (Allergan, Inc., Irvine, CA) participated in the design of the study, interpretation of the data, and preparation, review, and approval of the manuscript.

Conflict of Interest

Gail F. Schwartz has received consulting fees/honoraria from Allergan, Inc. Caroline Burk has received consulting fees/honoraria from Allergan, Inc. Teresa Bennett is an employee of Source Healthcare Analytics, which has received fees for data and statistical analysis from Allergan, Inc. Vaishali D. Patel is an employee of Allergan, Inc.

References

1. Congdon N, O'Colmain B, Klaver CC, Klein R, Muñoz B, et al. (2004) Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 122: 477-485.
2. Shields MB (2000) An overview of glaucoma. Textbook of Glaucoma. (4th edn), Lippincott, Williams & Wilkins, Philadelphia, pp: 1-2.
3. Friedman DS, Wolfs RC, O'Colmain BJ, Klein BE, Taylor HR, et al. (2004) Prevalence of open-angle glaucoma among adults in the United States. Arch Ophthalmol 122: 532-538.
4. Dietlein TS, Hermann MM, Jordan JF (2009) The medical and surgical treatment of glaucoma. Dtsch Arztebl Int 106: 597-605.
5. Le A, Mukesh BN, McCarty CA, Taylor HR (2003) Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. Invest Ophthalmol Vis Sci 44: 3783-3789.
6. The AGIS Investigators (2000) The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 130: 429-440.
7. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, et al. (2002) The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 120: 701-713.
8. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, et al. (2002) Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 120: 1268-1279.
9. Collaborative Normal-Tension Glaucoma Study Group (1998) The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol 126: 498-505.
10. Li T, Ervin AM, Scherer R, Jampel H, Dickersin K (2010) Setting priorities for comparative effectiveness research: a case study using primary open-angle glaucoma. Ophthalmology 117: 1937-1945.
11. Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, et al. (2001) Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology 108: 1943-1953.
12. Craven ER, Walters TR, Williams R, Chou C, Cheetham JK, et al. (2005) Brimonidine and timolol fixed-combination therapy versus monotherapy: a 3-month randomized trial in patients with glaucoma or ocular hypertension. J Ocul Pharmacol Ther 21: 337-348.
13. Sherwood MB, Craven ER, Chou C, DuBiner HB, Batoosingh AL, et al. (2006) Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. Arch Ophthalmol 124: 1230-1238.
14. Goñi FJ; Brimonidine/Timolol Fixed Combination Study Group (2005) 12-week study comparing the fixed combination of brimonidine and timolol with concomitant use of the individual components in patients with glaucoma and ocular hypertension. Eur J Ophthalmol 15: 581-590.
15. Khouri AS, Realini T, Fechtner RD (2007) Use of fixed-dose combination drugs for the treatment of glaucoma. Drugs Aging 24: 1007-1016.
16. Rossi GC, Pasinetti GM, Scudeller L, Radaelli R, Bianchi PE (2011) Do adherence rates and glaucomatous visual field progression correlate? Eur J Ophthalmol 21: 410-414.

17. Gray TA, Orton LC, Henson D, Harper R, Waterman H (2009) Interventions for improving adherence to ocular hypotensive therapy. Cochrane Database Syst Rev : CD006132.

18. Djafari F, Lesk MR, Harasymowycz PJ, Desjardins D, Lachaine J (2009) Determinants of adherence to glaucoma medical therapy in a long-term patient population. J Glaucoma 18: 238-243.

19. O'Hare F, Jeganathan VS, Rokahr CG, Rogers SL, Crowston JG (2009) Readability of prescription labels and medication recall in a population of tertiary referral glaucoma patients. Clin Experiment Ophthalmol 37: 849-854.

20. Higginbotham EJ, Hansen J, Davis EJ, Walt JG, Guckian A (2009) Glaucoma medication persistence with a fixed combination versus multiple bottles. Curr Med Res Opin 25: 2543-2547.

21. Patel SC, Spaeth GL (1995) Compliance in patients prescribed eyedrops for glaucoma. Ophthalmic Surg 26: 233-236.

22. Robin AL, Covert D (2005) Does adjunctive glaucoma therapy affect adherence to the initial primary therapy? Ophthalmology 112: 863-868.

23. Dunker S, Schmucker A, Maier H; Latanoprost/Timolol Fixed Combination Study Group (2007) Tolerability, quality of life, and persistency of use in patients with glaucoma who are switched to the fixed combination of latanoprost and timolol. Adv Ther 24: 376-386.

24. US Department of Commerce (2001) Profiles of General Demographic Characteristics: 2000 Census of Population and Housing, United States. Washington, DC.

25. Rylander NR, Vold SD (2008) Cost analysis of glaucoma medications. Am J Ophthalmol 145: 106-113.

26. Fiscella RG, Jensen MK (2008) Cost analysis of glaucoma medications. Am J Ophthalmol 145: 1108-1109.

27. Farris KB, Kaplan B, Kirking DM (1994) Examination of days supply in computerized prescription claims. J Pharmacoepidemiol 3: 63-76.

28. Grymonpre RE, Didur CD, Montgomery PR, Sitar DS (1998) Pill count, self-report, and pharmacy claims data to measure medication adherence in the elderly. Ann Pharmacother 32: 749-754.

29. Lo JC, Pressman AR, Omar MA, Ettinger B (2006) Persistence with weekly alendronate therapy among postmenopausal women. Osteoporos Int 17: 922-928.

30. Dezii CM, Kawabata H, Tran M (2002) Effects of once-daily and twice-daily dosing on adherence with prescribed glipizide oral therapy for type 2 diabetes. South Med J 95: 68-71.

31. Wogen J, Kreilick CA, Livornese RC, Yokoyama K, Frech F (2003) Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting. J Manag Care Pharm 9: 424-429.

32. Perreault S, Blais L, Lamarre D, Dragomir A, Berbiche D, et al. (2005) Persistence and determinants of statin therapy among middle-aged patients for primary and secondary prevention. Br J Clin Pharmacol 59: 564-573.

33. Perreault S, Blais L, Dragomir A, Bouchard MH, Lalonde L, et al. (2005) Persistence and determinants of statin therapy among middle-aged patients free of cardiovascular disease. Eur J Clin Pharmacol 61: 667-674.

34. Suh DC, Thomas SK, Valiyeva E, Arcona S, Vo L (2005) Drug persistency of two cholinesterase inhibitors: rivastigmine versus donepezil in elderly patients with Alzheimer's disease. Drugs Aging 22: 695-707.

35. Schwartz GF, Platt R, Reardon G, Mychaskiw MA (2007) Accounting for restart rates in evaluating persistence with ocular hypotensives. Ophthalmology 114: 648-652.

36. Stewart WC, Chorak RP, Hunt HH, Sethuraman G (1993) Factors associated with visual loss in patients with advanced glaucomatous changes in the optic nerve head. Am J Ophthalmol 116: 176-181.

37. Friedman DS, Quigley HA, Gelb L, Tan J, Margolis J, et al. (2007) Using pharmacy claims data to study adherence to glaucoma medications: methodology and findings of the Glaucoma Adherence and Persistency Study (GAPS). Invest Ophthalmol Vis Sci 48: 5052-5057.

38. Wilensky J, Fiscella RG, Carlson AM, Morris LS, Walt J (2006) Measurement of persistence and adherence to regimens of IOP-lowering glaucoma medications using pharmacy claims data. Am J Ophthalmol 141: S28-33.

39. Reardon G, Schwartz GF, Kotak S (2010) Persistence on prostaglandin ocular hypotensive therapy: an assessment using medication possession and days covered on therapy. BMC Ophthalmol 10: 5.

40. Schwartz GF, Quigley HA (2008) Adherence and persistence with glaucoma therapy. Surv Ophthalmol 53: S57-68.

41. Kulkarni SV, Damji KF, Buys YM (2008) Medical management of primary open-angle glaucoma: Best practices associated with enhanced patient compliance and persistency. Patient Prefer Adherence 2: 303-314.