

Compliance with Eye Care in Glaucoma Patients with Comorbid Depression

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ABSTRACT: **Background:** Comorbid depression may play an important role in non-compliance with medical treatment among patients with chronic illnesses. Glaucoma is a potentially blinding chronic disease requiring life-long commitment to medical therapy. Failure to adhere to anti-glaucoma treatment may lead to disease progression and visual loss.

Objectives: To assess the prevalence of depressive symptoms in glaucoma patients and the association between these symptoms and non-compliance with anti-glaucoma therapy.

Methods: In this cross-sectional observational study, compliance with pharmacotherapy was assessed with the Morisky Medication Adherence questionnaire (eight items). Screening for depression was performed by means of the CES-D (Center for Epidemiologic Studies Depression scale). The association between depression and compliance rates was analyzed.

Results: The study group comprised 76 glaucoma patients; 19.7% of the subjects were classified as non-compliant (Morisky cutoff < 10) and 21.1% suffered from depression (CES-D cutoff \geq 16). We found a similar level of non-compliance when comparing depressed with non-depressed glaucoma patients. However, a correlation was observed between the level of depression and the level of non-compliance ($P = 0.04$).

Conclusions: Our study revealed a similar rate of depression in glaucoma patients and the general Israeli population. The presence of depression was not associated with the presence of non-compliance, yet the level of depression was associated with the level of non-compliance.

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for nearly one-eighth of the cases [2]. Despite significant progress in the diagnosis and treatment of glaucoma, a high percentage of patients still lose their sight. One pertinent contributing factor to this problem is low compliance with anti-glaucoma treatment [3].

Estimates of compliance with pharmacotherapy in patients with glaucoma vary, the highest compliance rate being 77% [4,5]. Nearly half the patients with glaucoma or suspected glaucoma stop refilling their drug prescriptions within half a year of treatment, and only 37% continue refilling their prescriptions after 3 years of treatment. The lack of compliance with glaucoma treatment is important because it often results in visual loss [3]. The main cause for reduced compliance is forgetfulness [6]. Other causes include improper application of eye care, adverse effects of the medication, inconvenient follow-up visits, disbelief in treatment benefit, and termination of eye care prior to refilling the prescription [6].

Depression is a common condition that may be concurrent with many chronic illnesses, such as hypertension, cancer, lung and heart diseases [7]. In chronic patients, comorbid depression has been associated with reduced compliance with medical therapy [8]. Depressed patients are three times more likely to be non-compliant with medical treatment than non-depressed [9]. Furthermore, antidepressant treatment was found to improve compliance in patients with human immunodeficiency virus [10].

The prevalence of depression among patients with eye morbidity varies greatly in different studies. In some studies glaucoma patients were found to have a high prevalence of depression [11,12], while others showed no such association [5,13]. The aim of the present study was to assess the prevalence of depressive symptoms in glaucoma patients and the possible association between depression and non-compliance with anti-glaucoma therapy.

PATIENTS AND METHODS

This study was approved by the Institutional Review Board of the Wolfson Medical Center and adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability

It is estimated that over 60 million people worldwide currently suffer from glaucoma, of whom 4.5 million are estimated to become legally blind [1]. In Israel glaucoma was documented to be the third cause of blindness, accounting

and Accountability Act regulations. Written informed consents was obtained from all participants.

The patients were recruited from the outpatient clinics at the Wolfson Medical Center and Bat Yam Medical Center. The data were collected between June 2007 and March 2008. The inclusion criteria were diagnosis of glaucoma, age 18 years and above, and use of anti-glaucoma eye drops. Patients were excluded if they were unable to independently administer eye drops due to physical disability or cognitive impairment.

All subjects underwent comprehensive general and ophthalmic evaluation, including medical and ophthalmic history, best corrected visual acuity test, slit-lamp examination, intraocular pressure measurement, and Humphrey visual field test with Swedish interactive threshold algorithm (SITA) standard or FASTPAC 24-2 (Carl Zeiss Meditec, Dublin, CA, USA). All participants completed two questionnaires evaluating depression and compliance with glaucoma treatment.

Depression was evaluated by means of the Center for Epidemiologic Studies scale screening test (CES-D) [14]. It is a 20-item questionnaire with statements corresponding to characteristic symptoms of depression experienced during the week prior to completion of the scale. Every item is graded from 0 (experienced for less than 1 day) to 3 (experienced for 5–7 days). The final score ranges from 0 to 60. Scores of 16 and above are indicative of depression, while higher scores suggest a more severe depression. The CES-D has been well validated and widely used in research settings, including glaucoma studies [11,12,15].

Compliance was evaluated by means of the eight-item Morisky Medication Adherence Scale [16], which consists of seven yes/no questions, graded 1 or 0, respectively. The eighth question – "How often do you have difficulty remembering to take all your medications?" – is graded 1 (all the time) to 5 (never to rarely). Compliance scores range from 1 to 12. Scores of 9 and below indicate lack of compliance. The questionnaire was found to be reliable (alpha 0.83) and correlated with disease control and pharmacy refills [17,18].

The question "How often do you miss scheduled appointments?" was added to the questionnaire, adapted from the Hill-Bone Compliance to High Blood Pressure Therapy scale. It is scored 1 (never) to 4 (always) [19]. In order to assess the frequency of the medical follow-up the patients were asked an additional question: "How often do you meet your ophthalmologist?"

STATISTICAL ANALYSIS

Differences between groups were assessed with Student's *t*-test and the Mann-Whitney test. Exploratory analyses were conducted to recognize possible mediators or modifiers of compliance such as age, gender, marital status, place of birth, years of education, disease duration and severity,

type and number of eye drops, medical comorbidity, visual acuity, intraocular pressure, and ophthalmic procedures. The Kolmogorov-Smirnov test was used to examine the distribution of the continuous variables of the study population. Bivariate analysis using chi-square correlations and Spearman's rho tested the association between depression and compliance. *P* value of 0.05 was selected as the threshold of statistical significance. In addition, a linear regression model was constructed to determine the relationship between the level of depression and the level of compliance, controlling for potential confounding variables listed above.

RESULTS

Seventy-six glaucoma patients participated in this cross-sectional analysis. The patients had suffered from glaucoma for an average of 7.26 years (range 0.1–45 years) and were treated with one type of eye drops per day (median, range 0–4).

COMPLIANCE WITH GLAUCOMA TREATMENT

The average Morisky score was 10.21 (SD 1.73). Sixty-one patients (80.3%) were classified as compliant (Morisky score \geq 10) and 15 patients (19.7%) were non-compliant. The median Morisky score was 11 (range 10–12) among the compliant patients and 8 (range 2–9) in the non-compliant group. The median ophthalmic follow-up interval was 3 months (range 1–12 months). Only 13 patients (17.1%) reported that they had "sometimes" missed appointments.

• General and glaucoma parameters and compliance

There were no significant differences between the compliant and the non-compliant groups in any demographic characteristic [Table 1]. We observed that the visual field mean defect in the worse eye was statistically greater in the non-compliant patients. There were no significant differences between the compliant and non-compliant groups in visual acuities, intraocular pressure, ophthalmic procedures, type or number of drops of glaucoma eye treatment, better eye visual field parameters, or worse eye visual field pattern standard deviation [Table 2]. Compliance was marginally better when the treatment was identical in both eyes versus unilateral or different eyes (86.3% vs. 66.7% vs. 83.3% respectively, *P* = 0.06), although a linear result was not produced.

• Compliance and reported medical follow-up

A significant association was found between non-compliance and frequent medical follow-ups. Compliant patients met their ophthalmologist every 3 months (median, range 1–12), compared to every 2.5 months (median, range 1–12) for non-compliant patients (*P* = 0.04). No association was found between missing a scheduled ophthalmic appointment and the Morisky score.

Table 1. Compliance and patient demographics

	Non-compliant (N=15)	Compliant (N=61)	P value
Male/female ratio	5:10	35:26	0.09*
Age (mean ± SD)	71 ± 8.38	73.27 ± 11.28	0.46**
Marital status			0.4*
Married	9 (60%)	40 (65.6%)	
Divorced	2 (13.3%)	3 (4.9%)	
Widowed	3 (20%)	17 (27.9%)	
Single	1 (6.7%)	1 (1.6%)	
Country of origin			0.22*
Europe	4 (26.7%)	26 (42.6%)	
Balkan states	2 (13.3%)	10 (16.4%)	
Arab countries	9 (60%)	18 (29.5%)	
Caucasus	0	6 (9.8%)	
Latin America	0	1 (1.6%)	
Born in Israel	2 (13.3%)	12 (19.7%)	0.5*
Years of residence in Israel (mean ± SD)	49.46 ± 15.38	47.45 ± 19.8	0.71**
Years of education (mean ± SD)	9.2 ± 4.12	10.72 ± 4.48	0.23**
Medical comorbidity	13 (86.7%)	53 (86.9%)	0.9*
Sedative/antidepressant/neuroleptic drugs	4 (26.7%)	7 (11.5%)	0.21*
Treatment in hospital clinic	5 (33.3%)	19 (31.1%)	0.87*

SD = standard deviation * Chi-square tests ** Independent-sample two-tailed t-test

Table 2. Compliance and glaucomatous characteristics

	Non-compliant	Compliant	P value
Glaucoma (yrs), median (min-max)	4 (0.2–15)	5 (0.1–45)	0.7§
Past ophthalmic procedures			0.34†
None	4 (26.7%)	26 (42.6%)	
Not related to glaucoma	6 (40%)	24 (39.3%)	
Glaucoma related	5 (33.3%)	11 (18%)	
No. of drops in the more treated eye, median (min-max)	1 (0–4)	1 (1–4)	0.5§
No. of drops in the less treated eye, median (min-max)	1 (0–3)	1 (1–3)	0.8§
Treatment in both eyes			0.06†
Identical	7 (46.7%)	44 (72.1%)	
Unilateral	6 (40%)	12 (19.7%)	
Different	1 (6.7%)	5 (8.2%)	
Untreated	1 (6.7%)	0	
Type of drops per patient			
Alpha-agonist	3 (20%)	16 (26.2%)	0.74†
Beta-blocker	11 (73.3%)	14 (22.9%)	0.74†
Carbonic anhydrase inhibitor	7 (46.7%)	35 (57.4%)	0.45†
Prostaglandin analog	8 (53.3%)	37 (60.7%)	0.6†
Visual acuity in better eye logMAR, median (min-max)	0.18 (0–0.48)	0.2 (0–2)	0.35§
Visual acuity in worse eye logMAR, median (min-max)	0.5 (0.1–3.4)	0.39 (0–3.4)	0.45§
IOP in lower pressure eye (mmHg), median (min-max)	13 (2–20)	13 (8–22)	0.27‡
IOP in higher pressure eye (mmHg) median (min-max)	16 (12–34)	15.5 (8–24)	0.16§
Visual field test			
MD in better eye (mean ± SD)	-5.5 ± 4.19	-4.89 ± 4.79	0.66‡
MD in worse eye (mean ± SD)	-12.23 ± 6.32	-8.63 ± 6.01	0.05**
PSD in better eye (mean ± SD)	2.5 ± 2.88	3.04 ± 3	0.55‡
PSD in worse eye (mean ± SD)	6.53 ± 4.2	5 ± 3.61	0.17‡

IOP = intraocular pressure, MD = mean defect, PSD = pattern standard deviation, SD = standard deviation, logMAR = logarithm of the minimum angle of resolution

* Statistically significant

‡ Independent-sample two-tailed t-test

† Chi-square tests

§ Mann-Whitney test

DEPRESSION

The average CES-D score was 8.65 (SD 9.11). Sixteen patients (21.1%) were defined as depressed (CES-D score ≥ 16) and 60 patients (78.9%) were not depressed. The median CES-D score was 3 (range 0–3) among the non-depressed patients as compared to 22.5 (range 16–34) among the depressed patients.

• General and glaucoma parameters and depression

There were no significant demographic differences between the depressed and non-depressed groups, except for the duration of residency in Israel, which was longer among the depressed than the non-depressed patients (55.43 vs. 45.83 years, $P = 0.02$). There were no differences in the use of general medications, including oral beta-blockers, sedatives, antidepressants or neuroleptic drugs.

There were no significant differences between the depressed and non-depressed groups regarding visual acuity, intraocular pressure, visual field test, ophthalmic procedures, or monotherapy. No differences in the rate of depression were found when comparing the type of eye drops, including topical beta-blockers.

• Depression and compliance with treatment

Among the 16 depressed patients 4 were non-compliant (25%), while among the 60 non-depressed patients 11 were non-compliant (18.3%). The median Morisky score was 10 (range 7–12) among the depressed patients and 11 (range 2–12) among the non-depressed. The median CES-D score was 5 (range 0–34) in the compliant group and 6 (range 0–33) in the non-compliant group. No significant association was demonstrated between the presence of non-compliance and the presence of depression ($P = 0.55$). However, a correlation was found between the quotient of depression (CES-D score) and the level of non-compliance (Morisky score, $r = -0.23$, $P = 0.04$).

DISCUSSION

The present study examined the prevalence and the severity of depressive symptoms in patients with chronic glaucoma, as well as the influence of comorbid depression on compliance with anti-glaucoma treatment. One-fifth (21.1%) of the studied patients were found to be depressed. One-fifth (19.7%) of the patients in this cohort were non-compliant with anti-glaucoma medication. The existence of depression was not associated with reduced compliance. However, a correlation was demonstrated between the severity of depression and the level of non-compliance, hence the more depressive symptoms the patient had, the lower his or her compliance.

Evaluating compliance to treatment is challenging. There are various assessment methods, such as blood or urine drug level measures, pill count, electronic monitoring devices, patient interviews and pharmacy records [5,8,15]. Unfortunately,

most of these tools are inaccurate. Moreover, there are even fewer available reliable techniques when assessing topical eye treatments. Patients' self-report was found to underestimate the true rate of non-compliance when compared with medication monitors [20].

Studies that examined the rate of compliance in glaucoma patients used patient response to a single question (omitting over 10% of the weekly dose, or missing more than two drug doses a week), prescription refill patterns from the health insurance fund database, or electronic monitoring devices [5,11,12,15]. In our study we chose to use a detailed questionnaire, the eight-item Morisky Medication Adherence Scale, which has proven to be a highly reliable screening tool [18]. This scale performed comparably to electronic devices, yet it was never validated in comparison to an eye-drop electronic monitoring device [21]. Further studies should explore compliance with treatment using self-reports as compared to electronic measurements.

Using a single-question assessment, Pappa et al. [12] found a depression rate of 46% and a compliance rate of 58% among 100 Greek patients, concluding that there was an association between depression and lack of compliance. Jayawant et al. [11] examined the compliance of elderly glaucoma patients according to prescription refill patterns and found that the rates of depression and compliance were 9.27% and 49%, respectively. The researchers reported a 29% decrease in compliance among depressed patients.

In the current study, we discovered a much higher compliance rate (80.3%) than the aforementioned publications. This rate is also similar to the upper estimates of compliance in glaucoma, ranging from 49% to 77% [4,11,12]. This might explain the reduced coexistence of non-compliance and depression among our patients. The wide estimate of compliance may result from population differences or diversity in compliance measurement methods, especially since self-report questionnaires might overestimate compliance.

Similar to our study, other glaucoma studies [5,15] that used electronic monitoring devices to measure compliance did not find an association between compliance and depression. Friedman et al. [15] reported a compliance rate of 55.6% in 196 patients who completed 8 weeks of follow-up (only 69% of the original cohort). A univariate analysis found a correlation of depression with non-compliance, while an adjusted analysis did not find such a connection. Hollo et al. [5] found a compliance rate of 77% and a mild to moderate depression rate of 12.1% with no correlation between the two conditions.

In the present study glaucoma severity was associated with decrease in compliance. This correlates with previous reports describing reduced compliance in progressive disease [5,12]. The reduced compliance might have accelerated the disease progression, yet negative causality is also applicable: patients with severe glaucoma might have technical difficul-

ties in administering eye drops or feel desperate because of the alleged lack of treatment benefit and are consequently less compliant. The non-compliant patients had frequent medical follow-ups; this might also represent a more severe disease that required a frequent follow-up. It is known that an inadequate follow-up is a predictive factor for non-compliance [8]. No association was found between the duration of the glaucoma or missed appointments and the level of compliance, contradicting previous findings [8,12].

Different types of eye drops have been reported to yield varied compliance rates. Prostaglandins were suggested to have the highest compliance rate, as compared to beta-blockers, alpha-agonists, and carbonic anhydrase inhibitors [22]. Our study, similar to that of Pappa et al. [12], found no difference in compliance with treatment when comparing different types of eye drops. The use of different types of eye drops, including topical beta-blockers, had no influence on the rate of depression either, which was similar to previous reports.

The rate of depression among the study participants was 21.1%. This prevalence is similar to the reported rate of depressive symptoms in the general Israeli population, ranging from 14.3% to 24% [24,25]. Similarly, Wilson et al. [13] failed to observe an increase in depression rates among American glaucoma patients. Those authors reported depression rates of 7.4% and 13.3% in the glaucoma group and control group, respectively. Other studies reported depression rates of 12.1% and 9.27% among Hungarian and American glaucoma patients, respectively [5,11]. A Greek study found that 46% of 100 glaucoma patients were depressed, without comparison to a control group or to the general population [12].

In conclusion, lack of compliance was found to be associated with frequent follow-ups and a more severe decrease in visual field test results. The presence of depression was not found to be associated with the presence of non-compliance, yet the *level* of depression correlated with the *level* of non-compliance, or in other words, severely depressed patients tend to comply less with treatment. Therefore, caregivers should give special attention to this population group and provide them with the appropriate pharmaco-behavioral care required to increase their compliance.

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