

Identification of noncompliant glaucoma patients using Bayesian networks and the Eye-Drop Satisfaction Questionnaire

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Objective: To identify poorly compliant glaucoma patients, using the Eye-Drop Satisfaction Questionnaire (EDSQ).

Methods: This was an observational cross-sectional study with compliance data collected by an electronic monitoring device. Patients with primary open-angle glaucoma or ocular hypertension completed the EDSQ, a six-dimension self-reported questionnaire addressing “treatment concern”, “disease concern”, “patient–clinician relationship”, “positive beliefs”, “treatment convenience”, and “self-declared compliance”. A Bayesian network (BN) was applied to explore compliance associations with EDSQ.

Results: Among 169 patients who completed the EDSQ, 113 had valid Travalert® data, of whom 25 (22.1%) demonstrated low compliance. All six EDSQ dimensions were associated directly, or indirectly, with compliance. Two profiles exhibited low compliance, ie, patients aged younger than 77.5 years with a poor patient–physician relationship and self-declared poor compliance and patients aged older than 77.5 years with a poor patient–physician relationship and self-declared good compliance. The third profile showed high compliance, ie, patients aged younger than 77.5 years with a good patient–physician relationship and self-declared good compliance.

Conclusion: Our results confirm a central role for the patient–physician relationship in the compliance process. Age, self-declared compliance, and patient satisfaction with the patient–physician relationship are all dimensions worth exploring before glaucoma medication is switched or proceeding to laser treatment or surgery.

Keywords: glaucoma, compliance, risk factors, patient satisfaction

Introduction

Glaucoma is the second leading cause of blindness globally.¹ From 1991 to 1999, primary open-angle glaucoma prevalence increased from 4.6% to 13.8% among the elderly.² Its treatment is aimed essentially at lowering intraocular pressure (IOP) by eye drop instillations, reserving surgery or laser surgery for the most severe cases. Several classes of medicine are available, ie, prostaglandin analogs, miotics, beta-blockers, alpha-adrenergic agonists, and carbonic anhydrase inhibitors. Glaucoma treatment principles and options have been reported by the European Glaucoma Society.³ Successful treatment depends upon strict lifetime adherence to the instillation schedule. Thus, higher adherence is associated with better IOP control, on average,⁴ and a lower risk of eventual blindness.⁵ However, patients perceive few symptoms in the early stages, whereas eye drops (with potential side effects) are needed daily and may become a burden, leading to poor treatment adherence.⁶

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Adherence to treatment schedules has been examined by numerous studies in glaucoma, using various methods. For example, the medication possession ratio, determining the mean proportion of days during a given period when patients possess medication, was calculated from insurance claims or prescription databases,⁷⁻⁹ and from electronic devices capturing drop counts.¹⁰ Alternatively, patients' self-declared compliance was obtained from interviews¹¹⁻¹³ or standardized questionnaires.^{8,14-18} Another difference between studies were noncompliance criteria, eg, patients who missed more than two doses per week¹⁸ or possessed insufficient drops for the specified period (medication possession ratio < 1).⁵ With this array of methodology across different drug classes and countries, compliance rates varied from 59% to 77%.^{7,11,14,16,18-21} More informally, imperfect compliance is consistently reported among glaucoma patients.

To improve glaucoma care, it is critical to identify patients who may not adhere to treatment. Factors conducive to noncompliance have been explored. For example, complex dosing regimens have an impact on compliance.^{19,22} However, barriers cited by most studies relate to patients' perception and knowledge about their illness and its treatment.^{7,11,16,18} These considerations prompted the development of an Eye-Drop Satisfaction Questionnaire (EDSQ) which asks patients to self-report their satisfaction and compliance with topical ophthalmic treatments.²³ Replies to these questions should be relevant to an exploration of noncompliance in glaucoma patients.

A suitable technique for analyzing such data is a Bayesian network (BN) which facilitates the representation and manipulation of information. A BN is a directed acyclic graph representing relationships between variables (nodes in the graph) with a related set of conditional probability tables that characterize local dependencies between the various nodes. Hence, it provides a powerful tool to study interdependencies between complex processes, such as patient behavior. The objective of this study was to identify poorly compliant glaucoma patients by exploring EDSQ data.

Methods and materials

The present survey was conducted according to French law. The protocol was reviewed and approved by the Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé and the Commission nationale informatique et liberté.²⁴⁻²⁶ This research was conducted according to the tenets of the Declaration of Helsinki.²⁷

Patients and study design

This multicenter study was conducted in France by 17 ophthalmologists (at 17 sites) specializing in the treatment of glaucoma, who also prescribed Travalert[®], a computerized device that reminds patients to instill eye drops, assists with instillations, and records dosing times. The accuracy of Travalert for measuring treatment adherence has been described elsewhere.^{28,29} Ophthalmologists recruited patients who used the device and gave informed consent before participating. At the inclusion visit, the ophthalmologist completed a medical questionnaire for each patient. General comorbidities (cardiovascular, central nervous system, hepatic diseases, diabetes, pulmonary diseases, digestive diseases, others) and eye comorbidities (macular degeneration, diabetic retinopathy, retinal detachment, cataract, uveitis, others) were collected.

Patients included used the Travalert device for at least eight weeks, were 18 years of age or older, and diagnosed with either primary open-angle glaucoma (including juvenile glaucoma, exfoliative glaucoma, pigmentary glaucoma, or normal-tension glaucoma) or high IOP. Patients with secondary glaucoma (congenital glaucoma, inflammatory glaucoma, angle-closure or narrow-angle glaucoma following cataract surgery), or took an anticoagulant three times per day or more, and patients with chronic eye dryness requiring instillations of more than five drops a day, were excluded.

According to a previous clustering analysis, data collected with the Travalert device allowed the patient sample to be categorized according to three compliance profiles, ie, high compliance, moderate compliance, or low compliance.⁴

Eye-Drop Satisfaction Questionnaire

The EDSQ is a self-assessment questionnaire that assesses patient satisfaction and compliance with eye-drop treatment for glaucoma or IOP. Its development in France and the UK involved two steps. First, patient and clinician interviews were conducted to determine an appropriate conceptual model and obtain patients' ratings. Second, a comprehension evaluation was undertaken to ensure the questionnaire's clarity, ease of comprehension, and cultural equivalence.²³ The questions are scored on a 1-5 Likert scale.

A scoring algorithm for the 21-item questionnaire was also developed and shown to have satisfactory validity and reliability.³⁰ The EDSQ algorithm computes scores (0-100) for six dimensions of attitudes towards eye-drop treatment, ie, "treatment concern" (five items), "disease concern" (two items), satisfaction with the "patient-clinician relationship" (five items); "positive beliefs" (three items), "treatment

convenience” (three items), and “self-declared compliance” (three items). High scores represented high dimension concerns.

EDSQ data were collected at the follow-up visit when the Travalert data were collected from the patient.

Statistical analyses

Population analysis and oversampling strategy

Patients who completed the EDSQ and provided sufficient Travalert data to define their compliance profile were included in the analysis. An oversampling method was adopted to increase the ability of the BN to identify risk factors for noncompliance.³¹ This involved randomly selecting patients from the smallest group (low compliance) as successive replacements to create a sample equal to the largest group (high and moderate compliance). A uniform (all patients had the same probability to be sampled, without site stratification) sampling method was used because the small sample size did not authorize strong distribution estimates. The objective was to achieve a ratio of one patient with low compliance to one with high or moderate compliance.

Bayesian networks

A BN is a form of probabilistic graph, representing a joint probability distribution of a set of variables with explicit independency assumptions. It is a directed acyclic graph, ie, without cycles and has edges that are orientated. It is composed of a set of nodes (each node represents one variable modeling the process of interest) and a set of conditional probability tables encoding local dependencies between the nodes/variables. BNs are often used to identify structure of the information when very few hypotheses could be identified a priori.

A BN was constructed to identify poor compliers by discriminating between low-compliance and moderate- or high-compliance patients. Center was not included in the BN due to the numbers of patients per center being too small. The network structure (relationships between variables) was based on data by applying the “taboo order” algorithm to scores derived from the BN learning algorithm.³² A score denoted the minimum description length, and was two fold; the first part qualified the network with respect to its structural complexity and the second part measured the goodness-of-fit between the network and the data. With a given order of nodes, it is simple to determine the best BN, because each node looks to its best parent, ie, its immediate predecessor amongst all available nodes. The goal of taboo order is to search for the order of nodes resulting in the best BN value

(highest minimum description length score), and to this end uses taboo search.³³ This algorithm is fully driven by the data, is fully inferential, and with no clinical expert input. Missing data were inferred according to the expectation-maximization structural method. Because BN requires categoric variables, EDSQ scores were categorized by dichotomizing (thresholds were determined while estimating the BN) them according to a decision tree-based algorithm aimed at maximizing the detection of low compliance. Descriptive analyses were performed using SAS for Windows v9.2 (SAS Institute, Inc., Cary, NC) and BN was obtained using Bayesialab v4.6.1 (Bayesia, Mayenne, France).

Results

Of the glaucoma specialists, 88.2% were male, 29.4% worked in a public hospital setting, and had qualified on average 16.5 years earlier. They declared 36.7 visits per week for primary open-angle glaucoma and 11.4 for ocular hypertension. Among 179 patients screened, 169 (94.4%) completed the EDSQ at the visit. One hundred and forty patients (78.2%) used the Travalert, brought it back to the visit, with successful data transfer to the investigator computer. Among the 140 transferred files, 113 (80.7%) provided reliable data (compliance fully documented for at least eight weeks) sufficient for the classification algorithm. Technical criteria to participate to the clustering algorithm have been published elsewhere.⁴

Patient characteristics

The characteristics of patients meeting the inclusion criteria are presented in Table 1. The gender ratio was balanced, mean age was 65.1 years, 16.6% had undergone surgery for primary open-angle glaucoma, and 10.1% had received laser therapy. At the inclusion visit, worst eye mean IOP was 16.4 mmHg and best eye mean visual acuity was 8.80. The frequency of high compliance (56.6%) was much greater than that of low compliance (22.1%).

Bayesian networks

The BN (Figure 1) shows three nodes directly related to Travalert-identified compliance, ie, patient–clinician relationship, self-declared compliance, and age. Treatment concern has three drivers, which are disease concern, gender, and positive beliefs, and itself impacts on the patient–clinician relationship. Treatment convenience impacts on positive beliefs, which impacts upon self-declared compliance.

Two subgroups of patients had a noticeable distribution across groups defined according to treatment concern score (Table 2). First, women with a disease concern score >47.018

Table 1 Characteristics of patients included in the study (n = 169)

Age, years	MD	1	
	Mean (SD)	65.1	(11.8)
	Median (range)	67.5	(18–89)
Gender, n (%)	MD	1	
	Male	83	(49.1)
	Female	85	(50.3)
Comorbidities, n (%)	Ocular	19	(11.2)
	Other	50	(29.6)
	MD	1	
Nonmedicated treatment of glaucoma/intraocular high pressure, n (%)	Surgery	28	(16.6)
	Laser	17	(10.1)
Intraocular pressure, mmHg (worst eye)	MD	5	
	Mean (SD)	16.42	(3.87)
	Median (range)	16	(9–40)
Visual acuity ^a (best eye)	MD	13	
	Mean (SD)	8.80	(1.98)
	Median (range)	10	(1–12)
Compliance profiles, n (%)	MD	56	
	Low compliance	25	(22.1)
	Moderate compliance	24	(21.2)
	High compliance	64	(56.6)

Note: ^aDecimal scale.

Abbreviations: MD, missing data; SD, standard deviation.

were markedly more likely to have a treatment concern score of >24.197 than the total population. Second, patients with a disease concern score of <47.018 and a positive beliefs score >61.335 were also more likely to have a treatment concern score of >24.197.

When compared with the total population, a higher percentage of patients with a treatment concern score <24.197 had a patient–clinician relationship score >67.5 (Table 3). More patients with a treatment convenience score of <69.397 had a positive beliefs score <61.335 compared with the total analysis population (Table 4). A higher percentage of patients with a positive beliefs score <61.335 had a self-declared compliance score <89.583, as compared with the analyzed population (Table 5).

Compliance identified by Travalert was related to three variables, these being age, patient–clinician relationship, and self-declared compliance (Table 6). Three different combinations of these characteristics were relevant to low or high compliance, compared with the total sample (Figure 2). Low compliance was associated with two combinations; first, age <77.5 years, a self-declared compliance score <89.5, and a patient–clinician relationship score <67.5 and, second, age >77.5 years, a self-declared compliance score of >89.5, and a patient–clinician relationship score <67.5. By contrast, high compliance was associated with age <77.5 years, a self-declared compliance score >89.5, and a patient–clinician relationship score >67.5.

Discussion

The primary objective of this study was to identify glaucoma patients who adhered poorly to treatment by recording their

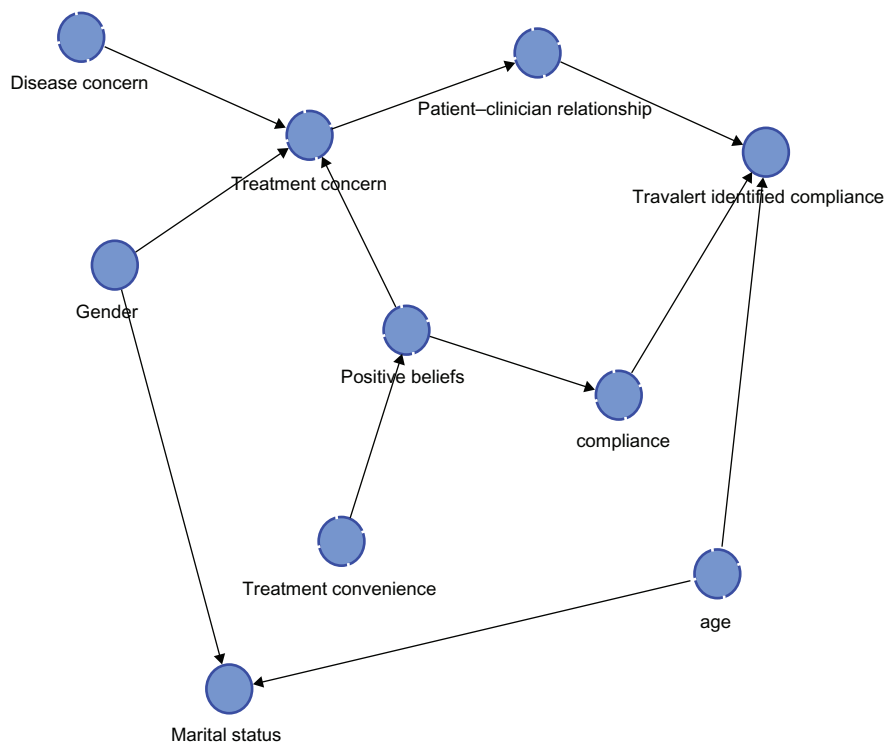


Figure 1 Bayesian network diagram predicting compliance as measured by Travalert®, obtained by oversampling data.

Table 2 Associations between treatment concern scores and positive beliefs scores, disease concern scores, and gender

Positive beliefs score	Disease concern score	Gender	Treatment concern score (n, %)			
			≤24.197		>24.197	
			n	(%)	n	(%)
≤61.335	≤47.018	Female	5	(55.6)	4	(44.4)
≤61.335	≤47.018	Male	9	(60.0)	6	(40.0)
≤61.335	>47.018	Female	5	(31.3)	11	(68.8)
≤61.335	>47.018	Male	10	(52.6)	9	(47.4)
>61.335	≤47.018	Female	16	(88.9)	2	(11.1)
>61.335	≤47.018	Male	31.5 ^a	(85.1)	5.5 ^a	(14.9)
>61.335	>47.018	Female	13	(36.6)	22.5 ^a	(63.4)
>61.335	>47.018	Male	21	(79.2)	5.5 ^a	(20.8)
Total			110.5 ^a	(62.8)	65.5 ^a	(37.2)

Notes: ^a0.5 frequencies due to missing data imputation. Eye-Drop Satisfaction Questionnaire scores ranged from 0 to 100. Higher dimension scores reflect more of the attribute implied by the name (eg, higher concern about disease). Threshold values fixed by the Bayesian network algorithm.

daily instillation times and eye drop counts objectively, with a computerized bottle holder (Travalert). In a previous analysis, patient demographics and baseline clinical parameters failed to discriminate between patients showing high, moderate, or low compliance.⁴ This second attempt enquired about attitudes towards treatment that might characterize poor compliers. This was explored with the EDSQ that examines patients' views about eye drop treatments, with aspects relevant to glaucoma, in order to explore compliance profiles. BN analysis was applied successfully to the EDSQ scores characterizing three compliance levels. The analysis identified two subgroups of patients at high risk of poor compliance when measured objectively; first, patients younger than 77.5 years of age with low self-declared compliance and an unsatisfactory relationship with their physician and, second, patients older than 77.5 years of age with high self-declared compliance and an unsatisfactory relationship with their physician.

These results confirm studies showing that communication and a good patient–physician relationship that provides

Table 3 Associations between patient–clinician relationship scores and treatment concern scores

Treatment concerns score	Patient–clinician relationship score (n, %)			
	≤67.5		>67.5	
	n	(%)	n	(%)
≤24.197	9	(8.1)	101.5 ^a	(91.9)
>24.197	24	(36.6)	41.5 ^a	(63.4)
Total	33	(18.8)	143	(81.2)

Notes: ^a0.5 frequencies due to missing data imputation. Eye-Drop Satisfaction Questionnaire scores ranged from 0 to 100. Higher dimension scores reflect more of the attribute implied by the name (eg, higher concern about treatment, a better clinician relationship). Threshold values fixed by the Bayesian network algorithm.

Table 4 Associations between positive beliefs scores and treatment convenience scores

Treatment convenience score	Positive beliefs score (n, %)			
	≤61.335		>61.335	
	n	(%)	n	(%)
≤69.397	38.5 ^a	(51.0)	37	(49.0)
>69.397	20.5 ^a	(20.4)	80	(79.6)
Total	59	(33.5)	117	(66.5)

Notes: ^a0.5 frequencies due to missing data imputation. Eye-Drop Satisfaction Questionnaire scores ranged from 0 to 100. Higher dimension scores reflect more of the attribute implied by the name. Threshold values fixed by the Bayesian network algorithm.

education for patients about glaucoma and its treatment is essential for compliance.^{8,11–13,16} Conversely, because patients rely strongly on their doctor for such information, a poor relationship was identified as a major barrier to compliance.^{8,11,12,16–18}

Interestingly, our results are not fully consistent with previous publications with respect to age and other factors associated with compliance. First, we found a relationship between age and compliance that was not observed in several studies.^{11,14,18,20,34} However, in contrast with customary statistical methods, we used BN based on association tables and inevitably model interaction effects between variables. Consequently, age was included with other factors (patient–clinician relationship and self-declared compliance), and was thereby related to objectively identified compliance (Travalert). Methods used in previous work may not have revealed such interaction effects.

Second, trust in the efficacy of treatment (closely related to our positive beliefs score) has been previously related to compliance,^{8,12} as have been concerns about disease⁵ and treatment convenience.^{12,34} Our BN analysis linked no equivalent EDSQ item directly to compliance. This difference may be explained by specific features of BN.

In our study, the absence of direct links between Travalert-identified compliance and previously identified components of compliance can be explained by the notion of conditional independence. The finding that only age, self-declared compliance scores, and patient–clinician relationship scores were

Table 5 Associations between declared compliance scores and positive beliefs scores

Positive beliefs score	Declared compliance score (n, %)			
	≤89.583		>89.583	
	n	(%)	n	(%)
≤61.335	31	(52.5)	28	(47.5)
>61.335	18	(15.4)	99	(84.6)
Total	49	(27.8)	127	(72.2)

Notes: Eye-Drop Satisfaction Questionnaire scores ranged from 0 to 100. Higher dimension scores reflect more of the attribute implied by the name. Threshold values fixed by the Bayesian network algorithm.

Table 6 Associations between Travalert® identified compliance and self-declared compliance scores, patient–clinician relationship scores, and age

Self-declared compliance score	Age	Patient–clinician relationship score	Travalert identified compliance (n, %)			
			Low		Moderate/high	
≤89.583	≤77.5	≤67.5	7	(87.5)	1	(12.5)
≤89.583	≤77.5	>67.5	24	(66.7)	12	(33.3)
≤89.583	>77.5	≤67.5	0	(0.0)	0.5 ^a	(100.0)
≤89.583	>77.5	>67.5	3	(66.7)	1.5 ^a	(33.3)
>89.583	≤77.5	≤67.5	8	(55.2)	6.5 ^a	(44.8)
>89.583	≤77.5	>67.5	19	(24.7)	58	(75.3)
>89.583	>77.5	≤67.5	10	(100.0)	0	(0.0)
>89.583	>77.5	>67.5	17	(66.7)	8.5 ^a	(33.3)
Total			88	(50.0)	88	(50.0)

Notes: ^a0.5 frequencies are due to missing data imputation. Eye-Drop Satisfaction Questionnaire scores ranged from 0 to 100. Higher dimension scores reflect more of the attribute implied by the name. Threshold values fixed by the Bayesian network algorithm.

linked directly to compliance indicates that compliance was conditionally independent of other BN variables. It does not mean that other variables were not involved in compliance indirectly. In fact, BN showed these scores to be indirect components of compliance by linkage through other variables. Thus, BN may provide a more precise description of the compliance process, and may show how different conceptions of compliance, finally impact on the behavior of glaucoma patients.

This study applied advanced techniques for data analysis, ie, BN and oversampling. The rationale for BN was that patients’ satisfaction and compliance with treatment is a

multidimensional phenomenon calling for methods that take complexity into account. Also, an oversampling strategy had to be introduced. The numeric imbalance between compliant patients and poorly compliant patients jeopardized the quality of our results, so we considered possible simple solutions to the problem, ie, oversampling (artificially increasing the size of the smallest group by random sampling and replacement), and undersampling (reducing the size of the largest group by randomly deleting cases). Despite evidence that undersampling has previously shown better results^{35,36} and that oversampling may increase the risk of overfitting,³⁷ the latter method had to be used because of our very small dataset, ie, only 113 patients

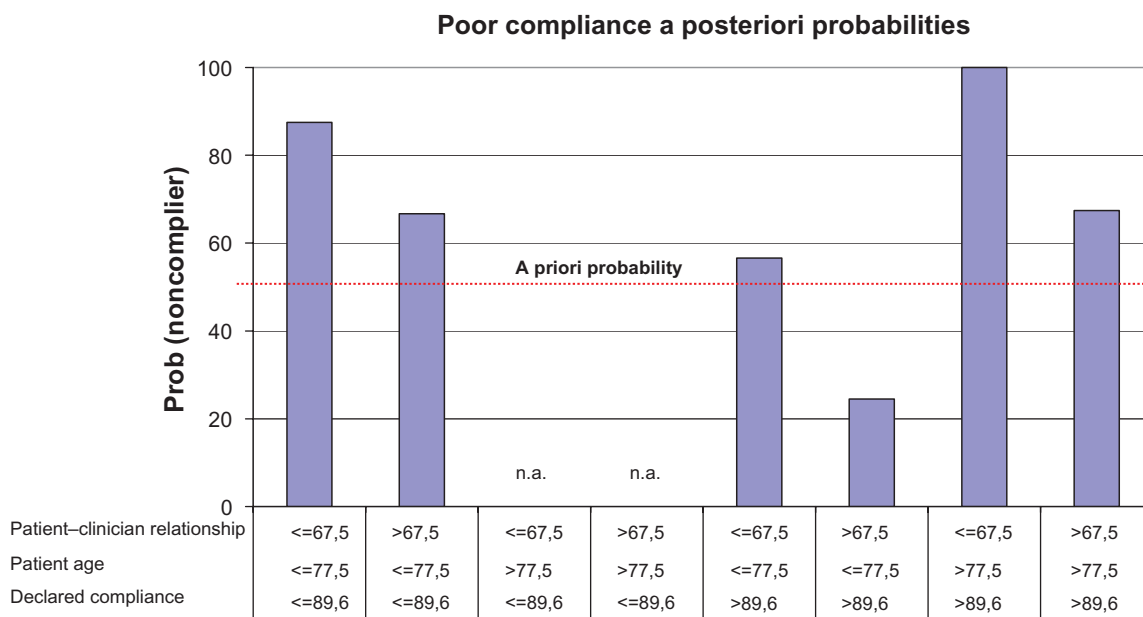


Figure 2 A posteriori probabilities of low compliance, according to age, patient–clinician relationship, and self-declared compliance. A priori probability was fixed at 50% as the result of the over sampling. Blue vertical bars represents a posteriori probabilities, once EDSQ results were estimated. The greater the distance from the red line to the bar chart, the greater the BN added value at determining patient compliance. EDSQ scores ranged from 0 to 100. Higher dimension scores reflect more of the attribute implied by the name. Threshold values fixed by the BN algorithm.

Abbreviation: n.a., not applicable.

provided sufficient data to construct a compliance profile, and the low-compliance group included only 25 patients.

The age and gender ratios of our sample are close to those of glaucoma-treated patients in France.³⁸ Whether these results could apply to other countries (within or even outside the European Union) is debatable, especially when some factors appeared to be culture-dependent, such as confidence in the doctor. Also, economic factors might play a role in this older population. For example, reimbursement status in France is almost independent of retirement, which is not the case in other countries. On the one hand, the EDSQ was developed according to a conceptual model and it was tested that this model applied in other countries. On the other hand, patient data collection will be requested to check whether this hypothesis will remain empirically valid.

We acknowledge that our study has certain limitations. First, our analyses were performed on a relatively small number of patients. Thus, the BN structure may have been biased by a few noncompliers. Also, only 113 (63.1%) patients of 179 were investigated for both EDSQ and compliance, possibly leading to selection bias, although internal validity (explored by the BN) might be less affected. We have not performed sample size estimation for a protocol aimed at confirming our findings without using the oversampling method. Microsimulation based on the BN described and accounting for the prevalence of poor compliance might be useful to fix the size of a future experiment. Second, we followed up patients who were willing to use Travalert, and these patients might have different behavior from that of the general population. Third, the results reported were observed in patients treated either by Travatan® or DuoTrav®, so extrapolation of the BN results to other drugs needs to be documented. Fourth, only one approach was adopted to elicit a BN structure. The small sample size of our survey did not allow for a test-retest-validation process. Hence, the resulting structure should be viewed with caution, and new surveys should be conducted to validate our findings. Also, it might well be worthwhile to undertake a validation of the structure, replicating our analysis with other structural learning algorithms and larger datasets. Finally, a question must be raised concerning our objective assessment of compliance. Electronic devices have been recognized as an efficient way to assess compliance,¹⁹ but they may have limitations. In particular, one reason for poor compliance encountered by some patients is difficulty with instilling eye drops correctly.^{13,18} Because Travalert counts only the number of drops dispensed by a bottle, and cannot verify that they are correctly instilled, our study could not control

this aspect of the research. Moreover, patients knew they were being observed, which might have impacted on their behavior. However, in a previous paper, we reported that these poor compliers had a significant increase in IOP (by about 2 mmHg) in comparison with good compliers. Therefore, this observational bias might have underestimated the impact of compliance on IOP control. Consequently, this BN identified poor compliers who had a lack of IOP control of at least 2 mmHg, which is a clinically relevant difference. Our sample size was not big enough to explore both the impact of clinician and patient characteristics on identifying poor compliers. In this approach, we favored data collected at a patient level. Additional research might be useful for identifying the correct information to be collected at an ophthalmologist level. These limitations warrant a cautious interpretation of our results and further work with a larger sample size and test-retest methodology to confirm the findings.

Conclusion

In conclusion, the application of BN to EDSQ data made it possible to re-examine the complex process of treatment compliance in glaucoma patients and to identify reasons for poor compliance. The crucial message for physicians from our results is that, before switching glaucoma treatments because of poor IOP control, they should consider the patient's age, self-declared compliance, and how best to educate the patient about glaucoma and its treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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