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Article

Noncompliance with drug therapy of glaucoma: a review about intervening factors

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Glaucoma is defined as an optic neuropathy, characterized for loss of visual field and injury of the optic nerve, being considered as the second cause of blindness in the world, which could be prevented by the use of antiglaucoma eyedrops. The lack of adhesion of the patient to the drug treatment can culminate with loss of the vision. The objective was to revise possible literature data regarding intervening factors for noncompliance and explain estimated rates of noncompliance. A systematic review about the subject was carried out in the period of January to June of 2006. Articles had been searched in two data bases, in the National Library of Medicine (PUBMED) and in the Literature Latin American and Caribbean Health Sciences (LILACS) using the following keywords: glaucoma, compliance of the patient, noncompliance of the patient, treatment and eyedrops. In PUBMED, 199 articles were collected, written in English and French languages. No article was found in LILACS. Considering the inclusion and exclusion criteria, 27 articles were selected, with 25 originals and two reviews. Twelve possible intervening factors for noncompliance were raised, as well as estimates for rates of noncompliance. The noncompliance rates varied from 4.6% up to 59%. Two factors, forgetfulness and inadequate between-doses interval, had been associated to noncompliance of the drug therapy. The factors race, adverse effects, treatment cost, number of instilled doses, coexisting illnesses and number of eyedrops used, had resulted contradictory, being impossible to affirm that they have contributed for noncompliance. Age, sex, educational level and loss of visual field, had not been associated with noncompliance. The glaucoma patients tended to disregard the drug treatment. The wide variation in noncompliance rates could be an influence from the authors' difficulty to define the noncompliance and the variety of methodologies used to estimate it. More studies are necessary for a better evaluation of these 12 raised factors.

Uniterms: Glaucoma/drug treatment. Drug treatment/adhesion. Eyedrops/use/evaluation.

O glaucoma é definido como uma neuropatia óptica, caracterizada por perda de campo visual e lesão do nervo óptico, sendo considerado como a segunda causa de cegueira no mundo, podendo ser evitada pelo uso de colírios antiglaucomatosos. A falta de adesão ao tratamento medicamentoso pode culminar com perda da visão. O objetivo do trabalho foi revisar dados da literatura a respeito de possíveis fatores intervenientes para a não adesão à terapêutica medicamentosa e relatar taxas de não adesão estimadas. Foi realizada uma revisão sistematizada sobre o assunto, abrangendo o período de janeiro a junho de 2006. Foram pesquisados artigos em dois bancos de dados, o da National Library of Medicine (PUBMED) e o de Literatura Latino Americana e do Caribe em Ciências da Saúde (LILACS), utilizando-se as seguintes palavras-chave: glaucoma, adesão do paciente, não adesão do paciente, tratamento e colírios. Foram levantados 199 artigos no PUBMED, nas línguas inglesa e francesa. Não foram encontrados artigos no LILACS. A partir dos critérios de inclusão e exclusão, foram selecionados 27 artigos, sendo 25 originais e duas revisões. Foram averiguados 12 possíveis fatores intervenientes para não adesão, bem como estimativas de taxas de não cooperação ao tratamento. As taxas de não adesão variaram de 4,6% a 59%. Dois fatores, 'esquecimento' e 'intervalo inadequado entre as doses', foram associados ao não-cumprimento da terapêutica medicamentosa. Raça, custo do tratamento, efeitos adversos, número de doses instiladas, doenças coexistentes e número de colírios utilizados tiveram resultados contraditórios, não podendo afirmar-se que os mesmos contribuíram para a não adesão. Idade, sexo, nível de escolaridade e perda de campo visual não foram associados à não adesão. Os pacientes glaucomatosos tenderam a descumprir o tratamento medicamentoso. A ampla variação nas taxas de não adesão pode ter sido influenciada pela dificuldade dos autores em definir a não adesão e pela variância de metodologias aplicadas para estimar a mesma. Mais estudos são necessários para uma melhor avaliação destes 12 possíveis fatores levantados.

Unitermos: Glaucoma/terapêutica medicamentosa. Tratamento medicamentoso/adesão. Colírios/uso/avaliação.

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INTRODUCTION

The glaucoma is defined, currently, as an optic neuropathy, characterized for loss of visual field and injury of the optic nerve (Rait, 2000), being the increase of the intra-ocular pressure (IOP) considered as a risk factor (Quigley, 1996). According to World Health Organization (WHO), glaucoma is the second worldwide cause of blindness (Kingman, 2004), with about 5.2 million blind people (Wilensky, 1996).

The blindness caused for this disease is irreversible (Coleman, 1999), being possible to prevent it through drug treatment with the use of eyedrops or surgical intervention. Normally, the first line of treatment is the drug therapy (Tsai *et al.*, 2003).

The success of the therapeutic drug depends strictly on the patient's compliance, that is, on the correspondence of patient's behavior when using the medicines, with the medical recommendations (Schwartz, 2005). The lack of fulfillment to the drug treatment can culminate with the patient's vision loss (Stewart, Konstas, Pfeiffer, 2004). This is a worrying fact, as Patel & Spaeth (1995) had found 59% of noncompliant patients. Some authors (Bloch *et al.*, 1977; Kass *et al.*, 1987; Patel, Spaeth, 1995; Nordström *et al.*, 2005) have found possible intervening factors for noncompliance to antiglaucoma therapy, with quite changeable results. In such a way, the proposal of this article is to make a review of literature data regarding the possible intervening factors for noncompliance to therapeutic regime, as well as, to find estimated rates for noncompliance.

MATERIAL AND METHODS

A systematic review about the subject was carried out in the period of January to June of 2006. Articles have been searched in two data bases, in the National Library of Medicine (PUBMED) and in the Literature Latin American and Caribbean Health Sciences (LILACS). The key words used in the research was: glaucoma, compliance of the patient, noncompliance of the patient, treatment and eyedrops. The search has included articles written in the English, French, Spanish and Portuguese languages, obeying the following priority order: glaucoma and compliance of the patient; glaucoma and noncompliance of the patient; glaucoma, compliance of the patient and eyedrops; glaucoma, noncompliance of the patient and eyedrops; glaucoma, compliance of the patient and treatment; glaucoma, noncompliance of the patient and treatment; compliance of the patient, eyedrops and treatment, and noncompliance of the patient, eyedrops and treatment. Articles published in the last 30 years were raised; between June, 1976 and June, 2006.

This review has included articles dealing with causes or intervening factors in the compliance to glaucoma drug treatment and estimated rates of compliance and/or noncompliance to glaucoma drug treatment; these articles were indexed to the used data base and had their available summaries over there. Those using invasive methods (methods using needles and/or catheters for blood collection with purpose of drugs dosage) for evaluation of the compliance; analyzing compared antiglaucomatous effect; approaching exclusively the persistence to glaucoma drug treatment of; focusing the improvement or increase of compliance to glaucoma drug treatment ; and having no known authorship were excluded. The interest data were collected and presented as text and tables.

Initially, 199 articles in the PUBMED, in English and French languages were raised. Articles in the LILACS were not found. Based on the inclusion and exclusion criteria, 27 articles were selected, being 25 originals and two reviews (Table I.)

The noncompliance rates found in this review varied from 4.6% to 59%, as demonstrated in Table II.

Twelve possible intervening factors had been found for noncompliance of glaucoma therapy: sex, age, race, adverse effect, number of instilled doses, number of used eyedrops, treatment cost, educational level, inadequate between doses interval, coexisting illnesses, forgetfulness and loss of visual field. The factors - forgetfulness and inadequate between doses interval- apparently contributed positively for noncompliance to glaucoma therapy.

Possible intervening factors

Sex

Bloch *et al.* (1977) had shown in their 40 patients study, that men adhere little to the antiglaucomatous treatment than women ($\chi 2 = 3.79$, $p < 0.1$). Patel & Spaeth (1995) suggested that men have higher trend to leave to use their eyedrops as compared to women, however, the cumulative data weren`t statistically significant ($\chi 2 = 1{,}35$, $p < 0{,}24$). Seven works pointed the inexistence of significant association of sex with noncompliance to treatment (Bour, Blanchard, Segal, 1993; Gurwitz *et al.*, 1993; Rotchford, Murphy, 1998; Gurwitz *et al.*, 1998; Kosoko *et al.*, 1998; Wane *et al.*, 2003; Khandekar, Shama, Mohammed, 2005).

Age

A study developed for Rocheblave (1983) in a French agricultural area, showed that patients aged more than 65 years cooperate better for the treatment, although the quantified data (in percentage) do not indicate this trend with precision. In another French work described for Bour; Blanchard and Segal (1993), the factor age does not significantly intervene

TABLE I - Selected articles for review study

Authors	Publication year
Bloch *et al.*	1977
Norell	1981
Granström	1982
Kass *et al.*	1982
Granström and Norell	1983
Rocheblave	1983
Granström	1985
Kass *et al.*	1986
Kass *et al.*	1987
Winfield *et al.*	1990
Bour *et al.*	1993
Gurwitz *et al.*	1993
Patel and Spaeth	1995
Gurwitz *et al.*	1998
Kosoko *et al.*	1998
Rotchford and Murphy	1998
Taylor *et al.*	2002
Tsai *et al.*	2003
Wane *et al.*	2003
Deokule *et al.*	2004
Stewart *et al.*	2004
Nordström *et al.*	2005
Khandekar *et al.*	2005
Olthoff *et al.**	2005
Robin and Covert	2005
Schwartz*	2005
Sleath *et al.*	2006

*Review articles

with patient's noncompliance (p = 0.42). Gurwitz *et al.* (1993) didn´t find significant difference in noncompliance between patients of different age strata: 65-74 years, 75-84 years and 85 years or more. Rotchford and Murphy (1998), Kosoko *et al.* (1998), Gurwitz *et al.* (1998), Wane *et al.* (2003), Khandekar, Shama & Mohammed (2005) and Sleath *et al.* (2006), have also concluded that age is not significantly associated with noncompliance.

Race

Gurwitz *et al.* (1993) divided the study participants in three racial groups: 'Caucasian', 'Afro-American' and 'others'. There was no difference in the compared noncompliance rates between the Caucasian and Afro-American groups. On the other hand, when these two groups were compared with the 'others' group, a longer and significant period of days without treatment was noticed in this last racial group. Patel & Spaeth (1995) compared the non-adhesion indexes between Caucasian and Afro-American, arriving at the conclusion that, statistically, the race would be a delinquent factor (limit) between compliance and noncompliance ($\chi 2 = 1.22$, $p = 0.27$). In another research of Kosoko *et al.* (1998), the races were compared in only two groups, black and non-black people. Cumulative results were analyzed by means of multiple logistic regression. This work concluded that race wasn´t a factor for noncompliance risk .

Adverse effect

Bloch *et al.* (1977) found that 7 (64%) not adherent and 9 (31%) adherent patients interrupted their treatment because of the adverse effect ($\chi 2 = 3.53$, $p < 0.1$). Granström & Norell (1983) noticed the occurrence of adverse effect in 54 of 78 patients using pilocarpine, but the non-adhesion rate wasn't significantly higher between patients exhibiting adverse effect ($p > 0.20$). Another study developed for Kass *et al.* (1987) pointed a higher adhesion on the part of patients using timolol maleate, when compared with those making use of pilocarpine, a fact related to the lower incidence of adverse effects of timolol maleate. Similarly to Bloch *et al.* (1977) study, Patel & Spaeth (1995) compared the presence of adverse effects in compliant and noncompliant patients, but, no significant influence for noncompliance was noticed ($\chi 2 = 1.42$, $p = 0.23$). Gurwitz *et al.* (1998), Rotchford & Murphy (1998) and Taylor, Galbraith and Mills (2002) have not correlated the presence of adverse effects with adhesion problems. Taylor, Galbraith and Mills (2002) verified that almost 10% of patients (2 in 21) left to use the eyedrops due to adverse effects. In a study on the classification of barriers for adhesion to glaucoma treatment, 27% of patients told that adverse effects confused or became difficult the use of eyedrops (Tsai *et al.*, 2003). Deokule, Sadiq and Shah (2004) noticed a prevalence of about 30% of adverse effects in the systemic level. Respiratory difficulty (14%), nocturnal dyspnea (7.6%), ankle edema (4%), and migraines (3.4%) were the most frequent events, suggesting that these effects could also have some contribution for noncompliance to the treatment. Sleath *et al.* (2006)pointed adverse effects as one of the main factors with respect to non-adhesion, being pointed by 16% of the patients.

Number of Instilled Doses

In a study of Norell (1981) where the patients used three times a day pilocarpine, it was noticed that evening doses were lost more frequently than morning ($\chi 2 = 115.35$, $p \sim 0$) and night doses ($\chi 2 = 61.82$, $p \sim 0$), indicating an adhesion improvement in drug regimens containing as a maximum

TABLE II - Rates of noncompliance to the drug treatment

Authors	Noncompliance rates	Methodologies	Definitions for noncompliance
Bloch *et al.*, 1977	27.5%	Interview	Loss of more than 1 dose per week
Kass *et al.*, 1982	41.8% 12.8%	Interview	Loss of more than 1 dose per month Loss of more than 1 dose per week
Kass *et al.*, 1986	24.5%	Monitor*	Loss of doses for one day in the month
Kass *et al.*, 1987	47.3%	Monitor*	Loss of doses for one day in the month
Winfield *et al.*, 1990	16%	Interview	Loss of 2 or more doses per week
Bour *et al.*, 1993	32%	Interview	Not defined
Gurwitz *et al.*, 1993	23.3%	Prescription dispensing	To leave to get a new prescription during the following 12 months after first lapse
Patel & Spaeth, 1995	59%	Interview	Not defined
Rotchford and Murphy, 1998	24%	Interview	Not defined
Gurwitz *et al.*, 1998	24.7%	Prescription dispensing	To leave to get medicines for at least 80% of the study days
Tsai *et al.*, 2003	8% 15%	Interview	Loss of 1 dose in 14 days Loss of 1 dose per week
Stewart *et al.*, 2004	34%	Interview	Not defined
Deokule *et al.*, 2004	13.8% 4.6% 4.6%	Interview	Loss of 1 dose in 14 days Loss of 2 doses in 14 days Loss of more than 2 doses in 14 days
Nordström *et al.*, 2005	50%	Prescription dispensing	To leave to get medicines for periods longer than 60 or 120 days (depending on the bottle size), in a period of 3 years.

* Device connected to eyedrops bottles, which memorizes (electronically) the number of drops and times that the eyedrops were instilled by the patient, storing the instillation schedules as well.

two daily applications. Granström & Norell (1983) have found good treatment adhesion independently of the number of daily applications. A comparison of two works, Kass *et al.* (1986) and Kass *et al.* (1987), disclosed that patients using pilocarpine four times a day had a lower adhesion rate than patients instilling maleate of timolol two times a day, 76% vs. 82.7%, respectively. Patients using the eyedrops more times a day, had a higher trend to disregard the treatment, as proven for Gurwitz *et al.* (1993). In this study, the patients who instilled eyedrops three or more times a day, exhibited a significantly higher rate of non-adhesion, as compared with those dripping eyedrops one or two times a day. Gurwitz *et al.* (1998) haven`t proved a significant association between the administration protocols and noncompliance.

Number of eyedrops

Granström & Norell (1983) have shown that the number of used eyedrops didn´t intervene on treatment non-compliance (r = -0.04). Kass *et al.* (1987) verified a higher adhesion rate to treatment with timolol maleate associated with other antiglaucomatous medicines, than when used separately, 86.1% vs. 78.6%, respectively. Patients dealing with a single medication are significantly more inclined to be non-adherent (Gurwitz *et al.*, 1993). In the Tsai *et al.* (2003) study, a half of patients stated that the application of a single eyedrops medication every day, does not facilitate the adhesion to therapeutic regimen. Amongst patients participating in this study, 86% had used more than one eyedrops medication every day. A study described by Robin & Covert (2005) concluded that the addition of a second medicine to therapeutics increased significantly the interval for the medicine dispensing, having a consequent decrease in adhesion ($p < 0{,}0001$). In a recent work, Sleath *et al.* (2006) got similar results as Granström and Norell (1983).

Treatment Cost

Kosoko *et al.* (1998), in a case-control study, have found four patients pointing the cost as intervening factor for non-adhesion. Amongst these patients, three were non-adherent. The statistical comparison of data wasn't possible

due to small number of involved patients. Patients thought the cost for acquisition of antiglaucomatous eyedrops medication was high, but they didn`t leave to use it due to this factor (Granström, Norell, 1983). On the other hand, patients told to leave the use the eyedrops medication, if their health plans left to pay for it (Tsai *et al.*, 2003). Khandekar, Shama and Mohammed (2005) verified that the treatment cost wasn`t a significant factor for noncompliance [RR =1.29; (95% IC 0.5-3.34)]. Nordström *et al.* (2005) concluded that, despite the higher cost of the prostaglandin-analog eyedrops, the patients using these medicines exhibited better adhesion as compared to those using β-blocker, α-agonist, miotic and carbonic anhydrase inhibitor eyedrops. Sleath *et al.* (2006) shown that 41% of patients had difficulty to pay for their eyedrops, pointing the treatment cost as one of the main factors related to noncompliance to treatment.

Educational Level

Five studies have shown that educational level did not contribute for noncompliance to drug treatment (Patel, Spaeth, 1995; Kosoko *et al.*, 1998; Wane *et al.*, 2003; Khandekar, Shama, Mohammed, 2005; Sleath *et al.*, 2006), in Wane *et al.* (2003) and Khandekar, Shama and Mohammed (2005) studies, it was noticed a considerable ratio of illiterates in the study samples, of 38.7% and 67.6%, respectively.

Inadequate between doses interval

Kass *et al.* (1982, 1986, 1987) and Granström (1982) have shown a trend of patients to instill eyedrops rejecting the schedules prescribed by doctors, with increase in the number instilled doses during the morning and evening periods. The inadequate interval between doses of antiglaucomatous eyedrops is a contributing factor for noncompliance, as disclosed for some studies (Patel, Spaeth, 1995; Kosoko *et al.*, 1998; Wane *et al.*, 2003; Khandekar, Shama, Mohammed, 2005).

Coexisting illnesses

Bloch *et al.* (1977) have significantly associated the presence of chronic illnesses, such as diabetes, hypertension, arthritis and atherosclerosis, with noncompliance to therapeutic drug ($\chi 2 = 4.36$, $p < 0.05$). Contrarily, Bour, Blanchard and Segal (1993) and Gurwitz *et al.* (1998) have not found significant differences correlating the presence of coexisting illnesses with noncompliance.

Forgetfulness

Bour, Blanchard and Segal (1993) have shown that 52.9% of the patients did not follow the treatment because they forgot to drip the eyedrops. Patel & Spaeth (1995) have statistically compared the forgetfulness with adhesion, and haven`t found a positive association for noncompliance to therapeutic drug ($p < 0.05$). The work of Taylor, Galbraith and Mills (2002) pointed out forgetfulness as the main reason for noncompliance to pharmacological treatment, being also this factor considered as a barrier with respect to adhesion, for Tsai *et al.* (2003). Sleath *et al.* (2006) have also associated forgetfulness with treatment noncompliance.

Loss of Visual field

Granström (1985) hasn`t verified significant statistical difference between the progression of visual field loss and noncompliance to drug treatment ($p = 0,54$). Similar result was obtained by Gurwitz *et al.* (1998).

DISCUSSION

The cumulative rates of noncompliance exhibited values between 4.6% and 59%. This ample variation could be, in part, due to different concepts and methodologies applied for noncompliance evaluation, showing also a patients trend to disrespect the treatment with antiglaucomatous eyedrops. In accordance with data raised from literature, eight of 12 possible intervening factors exhibited at least a story in literature trending to drug noncompliance. The factors 'forgetfulness' and 'inadequate between doses interval' seemed to positively contribute for noncompliance to therapeutic drug for glaucoma. Age, sex, educational level and loss of visual field were not significantly associated with noncompliance to drug treatment. Olthoff *et al.* (2005), in a review article, have found similar results about these factors.

Other possible intervening factors - race, adverse effects, treatment cost , number of instilled doses, number of used eyedrops, coexisting illnesses - resulted contradictory, being impossible to determine their actual intervenience for noncompliance to treatment. Amongst these factors, the 'number of used eyedrops' was the more conflicting one. In two works, Sleath *et al.* (2006) and Taylor, Galbraith and Mills (2002), the number of instilled eyedrops did not intervene for noncompliance. In other three works, Tsai *et al.* (2003), Kass *et al.* (1987) and Bour, Blanchard and Segal (1993), better adhesion was associated to the use of more than one eyedrops. Contrarily, Robin and Covert (2005) have shown that the addition of one medicine to therapeutics decreased the compliance. Some considerations could still be made respecting the factors 'adverse effects' and 'cost of the treatment'. The factor 'adverse effects', although not statistically associated to noncompliance, was described in some works (Taylor, Galbraith, Mills, 2002; Tsai *et al.,* 2003; Deokule, Sadiq, Shah, 2004; Sleath *et al.,* 2006) as one of the main barriers for the eyedrops instillation. Respecting to 'treatment cost' , this factor does not statistically intervene significantly for noncompliance, as demonstrated by Khandekar, Shama,

Mohammed (2005); however, as the supply of eyedrops medication was free of charge for individuals participating in this study, such situation could have influenced the statistical analysis of data. In the study developed for Sleath *et al.* (2006), where free of charge medicine supply didn't occur, 41% of the patients had difficulties to pay for their eyedrops.

CONCLUSIONS

The daily instillation of eyedrops is the main form of treatment of glaucoma, hindering the illness advance and preventing, consequently, the loss of vision in glaucomatous. Our literary review showed that glaucomatous patients have tended to do not fulfill adequately the drug treatment, as demonstrated by the found rates of noncompliance, which varied from 4.6% to 59%. This ample variation could be influenced by the difficulty, on the part of the authors, in defining noncompliance, and, even, by the variance of methodologies used for the determination of the noncompliance rates. Amongst the 12 possible factors raised as intervening for noncompliance, only two - 'forgetfulness' and 'inadequate between doses interval' - seemed to significantly contribute for noncompliance. The factors - 'treatment cost' and 'adverse effect' - although having not significantly been associated with noncompliance, have been pointed out as possible barriers the drug adhesion. It has been noticed that men tended to adhere little to treatment than women. More studies are necessary for a better evaluation of these possible intervening factors for noncompliance to glaucoma drug treatment.

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