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## **Adherence to Topical Medication in Patients with Inflammatory Eye Disease**

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**Running head:** Adherence in inflammatory eye disease

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**Key words:**

Adherence; topical medication; uveitis; ocular surface disease; patient education

## **Abstract**

### **Purpose**

To evaluate adherence to topical medication in patients with inflammatory eye disease.

### **Methods**

Questionnaire survey of patients attending inflammatory eye disease clinics. Treatment regimen was validated against hospital generated clinic letters.

### **Results**

There were 86 patients (52 uveitis and 34 ocular surface disease) with 30% (26/86) failing to identify one or more of the medications they were using, and 28% (24/86) unable to offer the correct indication for their treatment. A total of 64% (55/86) failed to use their medication as advised (27% on a daily basis); the commonest reason being forgetfulness. In patients using multiple eye drops, 26% left insufficient time intervals between successive eye drops, and 58% (50/86) reported not being given any instruction on drop instillation.

### **Conclusions**

We highlight poor adherence to topical medication in patients with inflammatory eye disease. We recommend a dedicated practitioner providing a proactive approach to patient education to improve adherence.

## Introduction

Inflammatory eye disease comprises a spectrum of potentially blinding conditions including uveitis and ocular surface disease (OSD). Patients frequently complain of painful, red eyes and reduced vision. Topical therapy is prescribed either on a limited or long-term basis, and often requires the instillation of multiple medications at varying frequencies throughout the day with the potential to lead to confusion and poor adherence that could significantly impact on prognosis. Commonly used preparations include corticosteroids, cycloplegics, ocular lubricants, anti-infectives and ocular hypotensives. Also, patients on long-term topical ocular hypotensives may develop OSD that will require additional treatment.<sup>1</sup>

Previous studies have demonstrated that patient adherence to topical medication in conditions, such as glaucoma can be poor and appears influenced by a number of factors, such as understanding of disease,<sup>2-4</sup> rationale of treatment,<sup>2,5,6</sup> having a simplified treatment regimen,<sup>7-10</sup> ease of drop instillation and whether they are dispensed in single use containers or multiple-use bottles.<sup>11-17</sup> In the ophthalmic literature there is very little information on adherence in inflammatory eye disease.<sup>18</sup>

We wished to evaluate adherence to topical medication in patients with inflammatory eye disease in a tertiary Eye Centre setting and to identify factors that may influence this.

Optimising patient adherence to medication can reduce the rate of preventable sight loss,<sup>19-22</sup> may have long-term financial economic benefits,<sup>19-21</sup> as well as improving patient knowledge and understanding of their condition.<sup>20-24</sup>

## Methods

Data were collected from adult patients attending follow-up appointments at the Uveitis and Ocular Surface Disease clinics, Birmingham & Midland Eye Centre between August 2018 and November 2018 who were using topical medication. A sampling frame of 9-10 am was taken for a morning clinic and 2-3 pm for an afternoon clinic. Patients were excluded if there were significant language or comprehension difficulties. A two-part questionnaire was designed based on previous adherence studies in glaucoma.<sup>4,24,25</sup> A clinician completed the questionnaire with each patient. Part 1 contained questions asking the patient's knowledge of their medication and their adherence to treatment:

- Name of topical medication(s) – non-proprietary (generic) or brand
- Indication(s) for use
- Which eye(s) they instilled the medication and frequency of use
- Time between instilling consecutive medication (where applicable)
- If they had received instructions on how to instill topical medication
- Self-reported estimations of adherence to treatment i.e. not using the medication and/or at the wrong frequency, including the previous 4-week failure rate
- The main reason for failure to adhere
- The use of reminder aides.

Part 2 was completed by the clinic doctor who entered the subtype of uveitis and OSD and the current topical therapy. Clinical diagnosis and treatment regimen were validated against clinic letters to the patient's General Practitioner generated by the Winscribe™ or

Medisoft™ hospital software after the patient's previous clinic attendance. All patients automatically receive a copy of this letter. The documented treatment was compared with the responses of each patient. Basic demographic data, such as gender, age and ethnicity were also collected.

The questionnaire was piloted on 5 uveitis and 5 OSD patients by clinicians with different levels of ophthalmological experience and modified as a consequence of their comments to show face validity.

The study was registered as an audit on the Clinical Effectiveness Department Safeguard Audit System with Sandwell and West Birmingham Hospitals NHS Trust (audit number 820).

## Results

A total of 86 patients were included (33 men and 53 women; age range 21-87 years, mean 50 years). The majority of patients were White 66% then Asian/Asian British 24% that reflects the typical case-mix of these clinics. There were 52 uveitis and 34 OSD patients. A breakdown of the subtypes of inflammation is shown in Table 1 and 2, respectively.

A total of 21 (24%) patients used topical medication in only one eye and the rest (65, 76%) in both eyes. There were 57/86 patients (66%) who were using more than one medication. The number of different topical medications used ranged from 1-10, mode 2 (24/86, 28%; Table 3). The medications included a large range of ocular lubricants, acetylcysteine, allogenic serum eye drops, non-steroidal anti-inflammatories, anti-allergy, ciclosporin, a variety of corticosteroids, ocular hypotensives, anti-infectives (antibiotics and antivirals), sodium chloride and cycloplegics. A total of 52 (60%) patients used preserved medications but in 50% of these, they used a combination of preserved and unpreserved medications as not all were available unpreserved. Of the 34 (40%) patients using only unpreserved medications, the majority (24/34, 71%) were in the OSD group.

There were 28/86 patients (33%) who failed to correctly name one or more of their topical medications, but 60/86 patients (70%) knew the clinical indication for all of their medications, 12/86 (14%) knew the clinical indication of some of their medications and 14/86 (16%) did not know the clinical indication for any of their medications.

The most common frequency of instillation was twice a day (24/86, 28%) but 25/86 (29%) patients were instilling treatment four or more times a day, with 8/86 (9%) eight or more

times a day (Table 4). When compared with the hospital generated letter 71/86 (83%) patients accurately stated the number of times a day they needed to use their medication, but 55/86 patients (64%) reported that at some period since they started using topical medication they had failed to use it as advised, with 15 patients (27%) estimating this to be on a daily basis (Figure 1). The most common reason offered being forgetfulness (26/55, 47%; Figure 2) despite 31/86 (36%) patients having some form of reminder aide with the majority 17/31 (55%) using an electronic device, such as a mobile phone. The mean failure rate over the previous four weeks was 37% (Table 5).

The majority of patients (49/86, 57%) had been using topical medication for more 10 years and only 5/86 (6%) patients had used them for less than one year. Yet 50/86 (58%) of patients stated they had never been given any instructions, verbal or written on how to instill topical medication. Of the 57 patients using multiple topical medications, 15 (26%) reported an insufficient time interval (< five minutes) between consecutive medications (Table 6).<sup>26</sup>

## Discussion

Adherence to medicines can be defined as the extent to which the patient's action matches the agreed recommendations. Adherence presumes an agreement between prescriber and patient about the prescriber's recommendations. Non-adherence may limit the benefits of medicines, resulting in lack of improvement, or deterioration, in health.<sup>27</sup>

At some period during their disease 64% of patients were non-adherent to their treatment. Studies on glaucoma have shown non-adherence of 4.6-80%<sup>25</sup> and even when medications are provided at no cost and patients are aware that they are being monitored, adherence rates were only approximately 70%.<sup>28</sup> Our patients were on multiple medications and this may be a factor for our poor adherence rates, as glaucoma studies have shown that patients were more adherent using fewer medications.<sup>8,29</sup> There was a mean 4-week failure rate of 37% that is higher than the 14% 2-week failure rate in one glaucoma study in patients who stated missing one dose of medication.<sup>2</sup>

In patients with inflammatory eye disease, one might expect good adherence if treatment is aimed at improving redness, pain, photophobia and restoring vision, but this must be balanced by patients having to take numerous medications, including cycloplegics that would blur vision, often instilling them many times during the day with complex dosing regimens. This is despite medical staff verbally informing patients in clinic and patients receiving letters after their clinic appointment detailing their treatment.

It was not surprising that 33% of patients failed to correctly name one or more of their topical medications as many drugs often have unpronounceable names. Yet in a Taiwanese

study on glaucoma 70% of patients were unable to name their topical glaucoma medications.<sup>4</sup> A total of 83% patients accurately stated the number of times a day they needed to use their medication, and this was higher than one glaucoma study where 52% of patients knew the correct frequency of instillation of their topical therapy.<sup>2</sup>

It is encouraging that 70% knew the clinical indication for all their medications, considering many patients were on multiple medications. It could be inferred that this cohort of patients has a reasonable understanding of their condition and contrasts with our previous study where 200 uveitis patients were asked 20 uveitis-specific knowledge questions and only 45 (21.5%) answered more than 50% of them correctly.<sup>30</sup> In our cohort poor patient knowledge may not be a major consideration in non-adherence as it is in glaucoma,<sup>2,5,24,29,31</sup> but it is possible that some patients may not understand the potential sight threatening consequences of their condition.

Wolfram *et al.* stated that the use of preservative-free products in glaucoma may provide adherence benefits.<sup>32</sup> In our patient cohort 60% were using preserved medications, yet we found only 5.5% non-adherent patients complained of medication side effects (Figure 2). It is unlikely that preservative toxicity was a significant factor for non-adherence in our patient cohort, particularly as 29% of patients were instilling treatment four or more times a day (Table 4).

Improper drop instillation has been cited as an important feature in non-adherence to glaucoma medications.<sup>11-17</sup> Although we did not directly observe patients instilling their medication, as only 42% stated they had received instruction on how to do so and 26% of

patients reported an insufficient time interval (< five minutes) between consecutive medications, then it is reasonable to assume some patients would be doing this incorrectly.

There are multiple barriers why patients do not adhere to their topical therapy in glaucoma<sup>3,9,10,20,33</sup> and one could extrapolate many of these to inflammatory eye disease. They can be grouped into four major types: medication regimen, patient factors, provider factors, and situational or environmental factors.<sup>9</sup> These include poor education, lack of motivation, forgetfulness, drop application, and other practical issues including delivery systems (single-use containers, multiple-use bottles),<sup>15</sup> together with specific individual and age differences.<sup>33</sup> Forgetfulness was the major reason stated for non-adherence in our study and this is well recognized in adherence studies in glaucoma.<sup>6,10</sup>

Cunningham Jr stated in regard to non-infectious ocular inflammatory disorders “My first priority is to achieve prompt and complete control of the inflammation. This requires not only making the correct diagnosis and selecting appropriate medications, but that the patient ultimately accepts and adheres to the recommended treatment. To this end, I spend considerable time discussing the risks, benefits and alternatives of various therapeutic options.”<sup>34(p814)</sup> He was referring to systemic therapy and in our inflammatory eye disease clinics we counsel our patients in an identical manner. Yet we may spend less time informing patients about topical therapy compared with systemic therapy, and higher quality information transmission between physicians and patients about new medications requires more time.<sup>35</sup> Or perhaps patients perceive this route of administration to be not as important as systemic therapy? One can monitor adherence in patients taking systemic therapy for inflammatory eye disease by measuring plasma drug levels, medication counting

and optimizing administration, such as the use of intravenous drugs,<sup>18</sup> but these are not appropriate for patients on topical medication.

Interventions to improve adherence in glaucoma include patient education, reminder devices and eye drop instillation training.<sup>15,20-24</sup> Boland *et al.* showed improved adherence to glaucoma medication with telephone or text medication reminders<sup>36</sup> and email reminders also improved adherence but only in younger patients.<sup>37</sup> These measures may not be practical if patients are using medication frequently throughout the day and on regimens that may require a complicated treatment taper or have poor eyesight or hearing. There are a number of Smartphone apps with reminders for eye drops, such as EyeDropAlarm™ that provides sound alert reminders for multiple drops as often as every hour if needed, but this is only available for iOS.

To improve adherence, we recommend a dedicated practitioner in the clinical environment, such as an ophthalmic pharmacist or nurse practitioner providing a more proactive approach to patient education of topical therapy (indication and treatment). This would include (a) pre-printed sheets with the non-proprietary (generic) and brand name of each medication, their indication, which eye they should be used for and the dosage regimen until the next clinic appointment. These would be handed to the patient before they left the clinic. Where applicable this would be translated into other languages, and (b) observation of the patient instilling the treatment, then teaching the correct technique, then re-observing the patient to ensure their technique was correct.

To our knowledge this is the first study on adherence to topical medication in patients with inflammatory eye disease. We have identified poor adherence in our patient cohort. As non-adherence to glaucoma medications is a global issue, it is likely that the responses from our patients would not greatly differ from patients with uveitis and OSD attending clinics at other institutions. Clinicians need to be aware of non-adherence in patients with inflammatory eye disease as it could affect patient outcomes.

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#### **Declaration of Interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**Table 1: Uveitis sub-type in 52 patients**

<b>Uveitis sub-type</b>	<b>Number</b>
Idiopathic acute anterior uveitis	21
Idiopathic panuveitis	14
Idiopathic intermediate uveitis	5
HLA-B27-related acute anterior uveitis	3
Sarcoidosis-related anterior uveitis	2
Fuchs' heterochromic uveitis	2
Juvenile idiopathic arthritis-related uveitis	1
Vogt-Koyanagi-Harada syndrome	1
Cytomegalovirus anterior uveitis	1
Tubulo-interstitial nephritis and uveitis	1
Dermatomyositis with retinal vasculitis	1

**Table 2: Ocular surface disease sub-type in 34 patients**

<b>Ocular surface disease sub-type</b>	<b>Number</b>
Primary Sjögren's syndrome	7
Atopic keratoconjunctivitis	6
Ocular mucous membrane pemphigoid	5
Infective keratitis	5
Stevens-Johnson syndrome	4
Meibomian gland disease	3
Neurotrophic keratitis	1
Penetrating keratoplasty for keratoconus	1
Keratoconjunctivitis	1
Conjunctival neoplasia	1

**Table 3: Patient report number of topical medications (n = 86)**

<b>Number of topical medications</b>	<b>Number of patients (%)</b>
1	20 (23)
2	24 (28)
3	18 (21)
4	12 (14)
5	7 (8)
6	2 (2)
7	1 (1)
8	0 (0)
9	0 (0)
10	1 (1)
No idea	1 (1)

**Table 4: Patient reported frequency of instillation of topical medication**

<b>Frequency of instillation</b>	<b>Number of patients (n = 86)</b>
Every other day	1
Once a day	9
Twice a day	24
Three times a day	12
Four times a day	10
Five times a day	2
Six times a day	4
Seven times a day	1
Eight times a day	5
More than eight times a day	3
As required	12
Patient unsure	3

**Table 5: Percentage failure rate to use topical medication as advised over the previous four weeks (4-week failure rate)**

<b>% failure (mean 37)</b>	<b>Number of patients (n = 86)</b>
0	36
1-10	21
11-20	3
21-30	3
31-40	3
41-50	5
51-60	0
61-70	0
71-80	1
81-90	1
91-100	13

**Table 6: Patient reported time waited between instilling consecutive medication**

<b>Time waited between instilling drops</b>	<b>Number of patients (n = 57)</b>
Did not wait	4
1 minute	2
2 minutes	5
3 minutes	2
5 minutes	16
10 minutes	12
15 minutes	1
20 minutes	2
30 minutes	5
60 minutes	8

## Figure legends

**Figure 1:** Frequency of self-reported failure in administering topical medication (n = 86)

**Figure 2:** Main reasons offered for failure to use topical medication (n = 55)