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ADHERENCE TO TREATMENT IN ALLERGIC RHINITIS USING MOBILE TECHNOLOGY. THE MASK STUDY

SHORT TITLE: ADHERENCE TO TREATMENT IN THE MASK STUDY

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Abstract

Background: Mobile technology may help to better understand the adherence to treatment MASK-rhinitis (Mobile Airways Sentinel Network for allergic rhinitis) is a patient-centered ICT system. A mobile phone app (the *Allergy Diary*) central to MASK is available in 22 countries.

Objectives: To assess the adherence to treatment in allergic rhinitis patients using the *Allergy Diary* App.

Methods: An observational cross-sectional study was carried out on all users who filled in the *Allergy Diary* from January 1, 2016 to August 1, 2017. Secondary adherence was assessed by using the modified Medication Possession Ratio (MPR) and the Proportion of days covered (PDC) approach.

Results: 12,143 users were registered. 6,949 users reported at least one VAS data recording. Among them, 1,887 users reported ≥ 7 VAS data. 1,195 subjects were included in the analysis of adherence. 136 (11.28%) users were adherent ($\text{MPR} \geq 70\%$ and $\text{PDC} \leq 1.25$), 51 (4.23%) were partly adherent ($\text{MPR} \geq 70\%$ and $\text{PDC} = 1.50$) and 176 (14.60%) were switchers. On the other hand, 832 (69.05%) users were non-adherent to medications ($\text{MPR} < 70\%$). Of those, the largest group was non-adherent to medications and the time interval was increased in 442 (36.68%) users.

Conclusion and clinical relevance: Adherence to treatment is low. The relative efficacy of continuous versus on-demand treatment for AR symptoms is still a matter of debate. This study shows an approach for measuring retrospective adherence based on a mobile app. This represents a novel approach also for analyzing medication taking behavior in a real-world setting.

Key words: mHealth, mobile technology, adherence, rhinitis, treatment, observational study

Abbreviations

AR: Allergic rhinitis

ARIA: Allergic Rhinitis and Its Impact on Asthma

MASK: Mobile ARIA Sentinel network

mHealth: mobile health

MPR: Medication Possession Ratio

OTC: Over the counter

PDC: Proportion of Days Covered

QOL: Quality of life

VAS: Visual analogue scale

Introduction

Globally, non-adherence to medications is a major obstacle to the effective delivery of health care. Medication adherence and medication persistence are two different constructs. Medication adherence is defined as an active, cooperative and voluntary participation of the patient on following recommendations from a healthcare provider. This is a multifactorial behaviour that involves three critical steps, including initiation, implementation and discontinuation (1). Medication

persistence refers to the act of continuing the treatment for the prescribed duration (2). In research employing electronic databases in pharmacies, primary adherence assesses whether the patient received the first prescription whereas secondary adherence is an ongoing process that measures whether the patient received dispensing or refills as prescribed during a defined observation period (3). Medication persistence implies that the patient must have exhibited at least primary adherence, as it cannot be measured unless the patient has received the first dispensing (3). The two most commonly used secondary adherence medication measures are the Medication Possession Ratio (MPR) and the Proportion of Days Covered (PDC) (2). These two measures are closely related as they are both refill record-based adherence measurements.

Many mobile phone apps are available to support people in taking their medications and to therefore improve medication adherence (4,5). However, a recent meta-analysis found that the majority did not have many of the desirable features and were of low quality (4).

It is known that adherence to treatment is low in allergic diseases and asthma (6,7). Mobile technology may help to better understand the adherence and its determinants as well how to improve adherence to treatment (8). MPR and PDC are of interest. They have been applied on mobile technology (9) but cannot be used directly in anonymized app users as there is usually no information on prescription. Thus, the concepts of MPR and PDC should be modified when using data gathered from such apps.

MASK-rhinitis (Mobile Airways Sentinel Network for allergic rhinitis) is a patient-centered ICT (information and communication technologies) system (10). A mobile phone app (the *Allergy Diary*) central to MASK is available in 22 countries. It has been validated (11) and was found to be an easy and effective method of assessing symptoms of AR and work productivity (11-14). MASK follows the checklist for the evaluation of Good Practices developed by the European Union Joint Action JA-CHRODIS (Joint Action on Chronic Diseases and Promoting Healthy Ageing across the Life Cycle) (15).

The aim of this study was to assess the adherence to treatment in allergic rhinitis patients using the *Allergy Diary* App.

Methods

Design of the study

An observational cross-sectional study was carried out on all users who filled in the *Allergy Diary* from January 1, 2016 to August 1, 2017. Five visual analogue scales (VAS) assessed the daily control of the disease (i.e. global evaluation of allergic symptoms, nose, eyes, asthma and work) (16). Since users are anonymized and cannot be contacted, we could not use an adherence questionnaire such as the Morisky (17,18). The paper was written according to the STROBE checklist.

Inclusion criteria: people who had allergic rhinitis, who used the Allergy Diary, who completed at least 7 days (not necessarily consecutive) of symptom recording (VAS global score), and who continued to use the same AR medication over the study period.

Setting

Users from 22 countries filled in the *Allergy Diary* (Table 4). The *Allergy Diary* is available in 16 languages (translated and back-translated, culturally adapted and legally compliant).

Users

All consecutive users who registered to the *Allergy Diary* were included if they had filled in the VAS global measured. The Allergy Diary is filled in independently from the presence/absence of symptoms. There were no exclusion criteria for participation in the Allergy Diary initiative. Basic demographic characteristics (age, sex, country and language) were recorded. The *Allergy Diary* was used by people who found it on the internet, Apple store, Google Play or in any other way. Some users were patients who were asked by their physicians to use the app. However, due to anonymization of data, specific information could not be gathered as previously described in detail (12,13). The diagnosis of allergic rhinitis is based on the question “I have allergic rhinitis” but all users had rhinitis symptoms (11-14).

Allergy Diary and outcomes

The *Allergy Diary* collects information on AR symptoms experienced (nasal and ocular), disease type (intermittent/persistent), how symptoms impact users' lives, and type(s) of AR treatment used. Geolocalized users assess their daily symptom control via the touchscreen functionality on their smart phone: they click on 5 consecutive VAS measures (VAS-global measured, VAS-nasal, VAS-

ocular, VAS-asthma and VAS-work). Levels range from zero (not at all bothersome) to 100 (very bothersome). Independency of VAS questions was previously assessed using the Bland and Altman regression analysis (13,19). Users input their daily medications using a scroll list which contains all country-specific OTC and prescribed medications available (Figure 1 online). The list has been populated using IMS data.

Some of the VAS data used in this study have been analyzed in other studies with a different aim including work productivity (12) and assessment of treatment or multimorbidity (papers submitted). Moreover, the time frame of the three other studies was different.

Ethics

The Allergy Diary is CE1 registered. The terms of use have been translated into all languages and customized according to the legislation of each country. This thereby allows the use of the results for research purposes. The data are anonymized - including the geolocalized data - using k-anonymity (20-22). An Independent Review Board approval was not needed for this observational study.

Assessment of adherence

1- Definitions used: Several adherence calculation methods are based on tablet counts, electronic monitoring by medication containers, patient diaries, and use of adjudicated prescription claims from administrative databases. However, using the *Allergy Diary*, MPR and PDC with the IPSOR terminology cannot be directly calculated using a classical method (23). They can however be approached. In the present paper, we used:

- **Proportion of medication possession ratio (modified MPR):** ratio of days that medication was reported to be used on days in a given time interval (see definitions 2 and 3 for further details)
- **Proportion of days covered over a time interval (modified PDC):** ratio of days that medication was reported to be used on days in the time interval between the first and the last record considered (i.e. the first and the last day in which the VAS about symptoms control is filled in)

2- Number of days with VAS reported: a cut-off of at least 7 records of VAS was set up to ensure an adequate amount of data which assess adherence. Therefore, only users matching this cut-off were enrolled/included in the study.

3- Predetermined Time interval: The first 14 records were analyzed since the duration of symptoms in AR is usually short (24):

- In users who reported 7 to 14 days of data/symptom recording, we analyzed the total number of days of recording.
- In users who reported over 14 days of data/symptom recording, only the first 14 were analyzed.
- Data in duplicate (reporting, for the same day, 2 assessments) and multiplicate (reporting, for the same day, more than 2 assessments) have occurred (<10% of subjects).
 - For 7 records, any duplicate led to the withdrawal of the user.
 - For 8 records, 1 duplicate was allowed.
 - For 9 records, 2 duplicates were allowed.
 - For ≥10 records, 3 duplicates were allowed.
 - Thus, all users with less than 7 records were withdrawn.

4- Medication possession ratio (modified MPR): We proposed that:

- The same rhinitis treatment should be used during the time interval. No change in treatment for rhinitis was accepted and change represents an exclusion criteria. However, treatment for asthma was not considered and may vary.
- Based on an accepted adherence level ≥70%, the minimum number of days of data recording/collection was determined (Table 1).
- The modified MPR score was calculated as:

$$\frac{\text{days of reported treatment}}{\text{time interval (as determined by predetermined time interval)}}$$

5- Proportion of days covered over a time interval (modified PDC)

Both continuous and discontinuous/intermittent reporting was monitored/evaluated. We defined 5 levels of adherence depending on the modified PDC (Table 2)

- The first and last days of data recording were identified and defined the time interval.
- The dates of reporting within the time interval were assessed and counted.

- For duplicates or multiples, the number considered was the exact number (1, 2, 3...).
- The modified PDC score was calculated as:

$$\frac{\text{days of reporting}}{\text{time interval (as determined by first and last day of use)}}$$

- A number of recorded days greater than the time interval considered indicates that the user is taking more drugs than the initial treatment. We used two levels of $PDC \leq 1.25$ (adherent user to time interval as defined by first and last days of recording and ≤ 1.5 (adherent or partly-adherent user to time interval as defined by first and last day of recording). Combining $PDC \leq 1.25$ or ≤ 1.5 with MPR values, 4 groups were defined (Table 3).

Biases

In this study, we did not include the types of treatment used due to the significant variability between treatment recommendations in different countries and no clear pattern of treatment being easily identified from the data collected.

Although MASK can be used to assess medication adherence, there are biases which should be considered: (i) In the literature, there is no clear definition on what is considered “adherent” or “non-adherent”, in terms of app usage; (ii) It is not known whether adherence with an app in any way reflects adherence with either medication or control; (iii) Users are anonymized, it is impossible to know how people use apps and the results may not reflect their daily AR management; (iv) It is possible that they take more medications than reported by the App as they may forget to register their daily symptoms.

Sample Size

In this exploratory study, all registered users who fulfilled the inclusion criteria over the study period were included in order to obtain the best possible estimates for the specified time window.

Statistical analysis

For normally distributed data, means and SD were used.

Results

Characteristics of the user

A total number of 12,143 users were registered in the *Allergy Diary* during the observational period. 6,949 users reported at least one VAS data recording. A total of 64,566 VAS recordings were made. Among them, 1,887 users reported ≥ 7 VAS data (Figure 1). There were 888 (47%) males and 999 (53%) females. They had a median age of 32 years (25-75 percentiles: 22-44 years). The repartition of user by country is presented in Table 4.

Overall results

Overall results are presented in Table 5. Only 136 (11.28%) users were adherent ($\text{MPR} \geq 70\%$ and $\text{PDC} \leq 1.25$). In addition, 51 (4.23%) users were partly adherent ($\text{MPR} \geq 70\%$ and $\text{PDC} = 1.50$), and 176 (14.60%) were switchers, defined as users who did not use the same medication but for the defined interval ($\text{MPR} \geq 70\%$ and $\text{PDC} > 1.50$). On the other hand, 832 (69.05%) users were non-adherent to medications ($\text{MPR} < 70\%$). Of those, the largest group was non-adherent to medications and the time interval was increased in 442 (36.68%) users.

For a number of days reported under 15 to 20, users were vastly non-adherent ($\text{MPR} < 70$). On the other hand, above this level, users were more adherent to medications (PDC) than before. It therefore seems that users who reported VAS levels over 15 days are more likely to be adherent. Moreover, the median level of time interval was different between groups, suggesting that discontinuous treatment is associated with poorer medication adherence.

Discussion

Our study was characterized by information retrieved from patients from 22 countries. To our knowledge, this is the first study to perform an evaluation of medication adherence based on data retrieved from a mobile app using a routine way/real life setting. This study shows the very low adherence to treatment in AR patients in a real-life setting.

Strengths and limitations

The strengths and limitations of this study are those of mobile technology, as previously discussed (12, 13, 25). There are potential measurement biases when using apps since the information collected is usually restricted and less complete than when using more detailed paper or web-based questionnaires. App users may be a selected subset and therefore not fully representative of all AR patients. Higher education or specific age ranges might apply. The study was not meant to be representative of the general population. Precise patient characterization is impossible via an App used in real life, but every observational study using the *Allergy Diary* gave highly consistent results with a clear clinical perspective (11-14). Users self-reported the diagnosis of rhinitis but this was confirmed by the questionnaire on rhinitis and conjunctivitis symptoms included in the App. Mobile technology is likely to become an important tool to better understand and manage AR and asthma.

Other limitations should also be considered. Among a high number of users, only a relatively low number were constantly filling information on treatment in the app and we only considered users reporting over 6 days. We did not analyse the type of treatment due to its great variability. This will be done when more data become available and using machine learning approaches. Another limitation is that the app is based on the unsupervised input of data. There is, therefore, a bias related to potentially missing data input. Nevertheless, our study took the opportunity of analysing real-world adherence and designing new methodologies for analysing such data.

We did not include a questionnaire on medication adherence since users report their daily medications.

Discussion of results

Our data show that about 70% of AR patients filling data over 6 days (27.2% of the entire database) are non-adherent to medications. Only 11.3% of AR users filling data over 6 days were fully adherent to medications and time interval ($MPR \geq 70\%$ and $PDC \leq 1.25$).

Few studies reported the prevalence of adherence in AR patients in the real-life context. 35% of patients were non-adherent for some time during the treatment and 38% indicated that they discontinued treatment when they felt better (26, 27). One study, carried out in the outpatient setting, suggests that a short message service (SMS) helps to improve AR treatment (28).

Adherence in randomized control trials is high but does not reflect the real-life situation (29,30) and alternative measurement of adherence in a real-life setting is needed. The best studies would be using electronic devices that count and record the drugs taken. However, these devices are expensive and, as such, not a viable solution for large studies in AR patients (31). Considering that we live in an era of "digital revolution" and that a huge percentage of people have a smartphone, mobile applications appeared as a good alternative to improve patient control over their illness. Such m-health technology has enormous potential to be used as a reliable, cost-effective and usable tool, not only for AR, but also for other diseases (26,32,33). Although there are already some m-health tools for allergic rhinitis, there are few studies evaluating their benefits and impact (26). There is a growing understanding of barriers to adherence and ways to overcome them. The development of mAdherence tools to explore barriers to maintaining engagement is growing and will be important in the development of mHealth interventions.

There is no gold standard for measuring adherence to medication. There are mainly direct and indirect measures. All methods have their limitations, so it is highly recommended to combine more than one (34). In this study, we used a combination of MPR and PDC, the most used measures of secondary adherence. We defined adherence as $MPR \geq 70\%$ and $PDC \leq 1.25$. Results were grouped by PDC value by using a cut-off value of 1.25. Therefore, the resulting groups had $PDC \leq 1.25$ and $PDC > 1.25$ respectively. It was possible to verify that, although with some differences, both follow the same trend. Under 15 to 20 days, patients were mostly non-adherent, and there are some theories that can explain this such as that for many patients AR is only intermittent and that the most troublesome symptoms can be managed with a short course of medication. There are several subtypes of allergic rhinitis and, depending on the type and severity of the condition, the treatment may be different. AR can be described as a seasonal condition, therefore some patients may present persistent symptoms while others may present symptoms only when the allergen is present. On the other hand, above 15 days of VAS reported, patients tend to be more adherent, which may also be a result of more severe symptoms, leading to continuous treatment (27, 35) or to a better adherence in people reporting longer periods of use. It would be important to also study the attitudinal and behavioural clusters of individuals who continue to monitor and treat their AR above 15 days. Insights from research in asthma suggest that determining attitudinal clusters can provide insights into medication use and taking behaviour (36). All the participants were volunteers and anonymous, making them very remote from direct clinical input. Also, patients had no sense of being watched over (Hawthorn effect) which prevents a biased increase in adherence. In RCTs, adherence is likely to be much higher (37). Further research is needed to understand how patients can be motivated to use and app regularly and the role of the healthcare professional in suggesting that the app is used

as a means of assisting the patient to better understand their disease, monitor their symptoms and promote adherence.

Conclusion

This is the first paper to present adherence to AR treatment in a real-world setting from a European population sample. From a methodological point of view, this study highlights the opportunity to measure secondary adherence from an app (modified MPR and modified PDC). From a clinical point of view, this study gives the opportunity to discuss the gap that exists between theory and real world evidence, based on data from real practice, paving the way for a change management in allergic rhinitis. Further information will derive from the ongoing recruitment of Allergy Diary users. AR treatment is based on concepts that do not necessarily apply to real life. All recommendations propose a continuous treatment rather than an on-demand use (38). Our results show that adherence to treatment is low. The relative efficacy of continuous versus on-demand treatment for AR symptoms is still a matter of debate (39). In general, medical use (if achieved), non-anonymised and linked to the patients' electronic health-records, may be higher because of the Hawthorn effect (40,41). However, a requirement to use the app to gain assistance should always be offered without any coercion. In other words, careful patient counselling is required. Moreover, in real life, patients rarely follow treatment indications (guidelines). Finally, the use of such an app in the context of routine clinical care may present the opportunity to describe different Allergic Rhinitis (and Non-Allergic Rhinitis) phenotypes, each of which may potentially have its own adherence pattern (to app usage and treatment) and may ultimately help to identify early on which patients might benefit from specialist assessment.

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Table 1: Modified MPR cut-off for the assessment of medication adherence

Time interval*	Data on treatment*	Medication adherence** (Modified MPR)
7	5	71.4%
8	6	75.0%
9	7	77.8%
10	7	70.0%
11	8	72.7%
12	9	75.0%
13	10	76.9%
14	10	71.4%

*: Results expressed in days. **:accepted cut-off for adherence is Modified MPR > 70%

Table 2: Number of days assessed to calculate the modified PDC

Time interval*	1	1.25	1.5	2	≥2
7	7	9	10	14	≥15
8	8	10	12	16	≥17
9	9	11	13	18	≥19
10	10	12	15	20	≥21
11	11	14	16	22	≥23
12	12	15	18	24	≥25
13	13	16	19	26	≥27
14	14	17	21	28	≥29

*Results expressed in days

Table 3: Definition of groups for adherence

PDC Criteria	MPR Criteria	Descriptor	
≤ 1.25 or 1.5	≥ 70%	Users who always used the same medication for the defined time interval	Adherent user
≤ 1.25 or 1.5	<70%	Users who always used the same medication but at a time greater than the defined time interval	Partly adherent user
>1.25 or 1.5	≥ 70%	Users who did not use the same medication for the defined interval	Non-adherent user
>1.25 or 1.5	< 70%	Users who did not use the same medication and at a time greater than the defined time interval	Non-adherent user

Table 4: Repartition of users per country

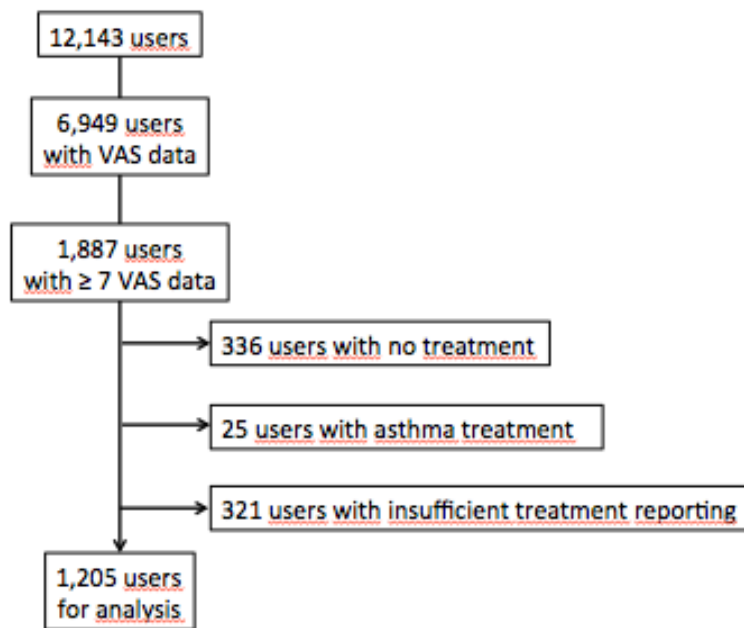
Country	Users
Australia	11
Austria	51
Belgium	15
Brazil	98
Canada	3
Czech Republic	3
Denmark	19
Finland	50
France	53
Germany	172
Great Britain	97
Greece	78
Italy	228
Lithuania	149
Mexico	344
Netherlands	46
Poland	75
Portugal	183
Spain	157
Sweden	15
Switzerland	32
Turkey	8
Total	1887

Table 5: Overall results: number of users depending on MPR, PDC and duration of reporting

Modified MPR	≥70%					<70%					Total users
	1	1.25	1.5	2	>2	1	1.25	1.5	2	>2	
7 days	4	5	5	5	11	6	5	5	10	41	97
8 days	3	3	6	5	11	2	14	8	4	41	97
9 days	0	1	2	1	25	1	2	6	4	35	77
10 days	5	2	0	2	8	2	4	6	10	32	71
11 days	2	2	0	2	10	2	2	1	7	19	47
12 days	0	2	0	2	5	0	2	18	3	12	44
13 days	0	0	1	3	11	1	5	2	10	16	49
14 days	0	3	1	7	8	2	3	7	6	17	54
15 days	0	2	2	0	3	2	5	1	5	13	33
16 days	0	1	2	1	6	4	3	6	3	9	35
17 days	0	1	4	3	3	2	3	6	4	7	33
18 days	2	2	1	0	3	4	1	1	2	7	23
19 days	0	3	3	2	2	1	3	2	1	3	20
20-22 days	5	6	2	4	3	7	10	12	4	14	67
23-24 days	7	1	5	0	4	7	2	4	6	7	43
25-29 days	2	5	3	1	4	10	15	16	3	8	67
30-34 days	5	9	4	4	4	9	10	11	9	12	77
35-39 days	3	3	1	1	0	12	8	7	5	8	48
40-49 days	5	7	2	3	3	12	7	8	11	10	68
50-59 days	3	5	0	2	1	7	13	4	5	3	43
60-74 days	5	9	3	2	0	4	13	1	4	3	44
75-99 days	4	6	4	1	0	6	10	5	4	4	44
>100 days	1	2	0	0	0	3	7	0	0	1	14
Total users	56 (4.68%)	80 (6.69%)	51 (4.26%)	51 (4.26%)	125 (10.46%)	106 (8.87%)	147 (12.30%)	137 (11.46%)	120 (10.04%)	322 (26.94%)	1195 (100%)

Data are reported in user

Figure 1: Flow chart of users



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CONFLICT OF INTEREST :

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