


REVIEW ARTICLE

A systematic review of factors influencing treatment adherence in chronic inflammatory skin disease – strategies for optimizing treatment outcome

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Abstract

Adherence describes how a patient follows a medical regime recommended by a healthcare provider. Poor treatment adherence represents a complex and challenging problem of international healthcare systems, as it has a substantial impact on clinical outcomes and patient safety and constitutes an important financial burden. Since it is one of the most common causes of treatment failure, it is extremely important for physicians to reliably distinguish between non-adherence and non-response. This systematic review aims to summarize the current literature on treatment adherence in dermatology, focusing on chronic inflammatory skin diseases such as psoriasis, atopic dermatitis and acne. A systematic literature search was performed using the PubMed Database, including articles from 2008 to 2018. Low treatment adherence is a multidimensional phenomenon defined by the interplay of numerous factors and should under no circumstances be considered as the patient's fault alone. Factors influencing treatment adherence in dermatology include patient characteristics and beliefs, treatment efficacy and duration, administration routes, disease chronicity and the disease itself. Moreover, the quality of the physician-patient relationship including physician-time available for the patient plays an important role. Understanding patients' adherence patterns and the main drivers of non-adherence creates opportunities to improve adherence in the future. Strategies to increase treatment adherence range from reminder programs to simplifying prescriptions or educational interventions. Absolute adherence to treatment may not be realistically achievable, but efforts need to be made to raise awareness in order to maximize adherence as far as possible.

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Introduction

Three different terms are used in the literature to describe to which extent a patient's behaviour corresponds with the advice given by a healthcare provider: Compliance, adherence and concordance.^{1–6} These three terms are often used interchangeably, but they reflect different philosophies of the physician-patient relationship.^{5,7} It can be difficult to accurately compare studies on this topic, since the terminology used differs amongst authors.

Until around 2003, the term compliance was most widely used in the literature. Compliance implies an authoritarian, asymmetric physician-patient relationship, in which the doctor has the exclusive decisional power. Physicians give instructions and patients are passive recipients and should follow the

prescribed regime without deviation. The word compliance may have negative connotations as it requests a submissive and obedient patient.^{8,9}

The concept of an appropriate physician-patient relationship has substantially changed in the last years, since patients have gained more autonomy. This paradigmatic shift is reflected by the new term adherence,¹⁰ which is nowadays preferably used.¹¹ The concept of adherence is based on a partnership between physician and patient, where both parties are actively involved in finding a mutual treatment agreement.^{12,13}

The word concordance, which originated in British literature, goes even further and places the patient in the centre of the decision-making process. It focuses less on compliance and more on overall success of treatment as a shared goal.^{12,14,15}

In this review article, only the term adherence will be used. Adherence can be divided into primary and secondary adherence. Primary adherence describes pharmacy refill records, whereas secondary adherence means the correct administration and continuation of a prescribed treatment.¹⁶

Poor treatment adherence is a complex and challenging problem of international healthcare systems, as it not only compromises patients' safety, but also constitutes a substantial financial burden. The annual costs related to medication non-adherence are estimated to range from 100 to 290 billion US\$ in the United States¹⁷ and approximately 1.25 billion € in Europe.¹⁸ In the era of cost-effectiveness, the research interest in this field has dramatically increased. Studies have shown a median adherence rate of 50% among patients with chronic illnesses.^{1,8,19} This alarming number illustrates the importance of reliably distinguishing non-adherence from non-response, because 'drugs don't work in patients who don't take them'.^{19–21} Non-adherence represents one of the most common causes of non-response to medication,^{22,23} and is frequently mistaken as drug failure when insufficient care is devoted to assessing patients' adherence to treatment. This wrong assumption may lead the physician to unnecessarily modify treatment or increase medication dose. Therefore, treatment adherence plays an essential role in the outcome of medical care.

Aims

Although the impact of treatment adherence has been extensively studied for chronic diseases including hypertension,^{24,25} diabetes mellitus,²⁶ epilepsy²⁷ and HIV,²⁸ there are only few studies addressing this topic in dermatology. Here, we review systematically the current literature on treatment adherence in chronic inflammatory skin diseases such as psoriasis, atopic dermatitis and acne.

Methods

Using the PubMed database, a literature search was conducted to identify clinical studies and review articles that assessed treatment adherence in chronic inflammatory skin disease. Specifically, we analysed reported methods used to measure adherence, factors influencing adherence and strategies used to improve treatment adherence. The research was limited to English, French or German language articles published between 2008 and 2018. The following keywords were used to perform the literature search: [compliance (TI) OR adherence (TI) OR non-adherence (TI)] AND (psoriasis OR atopic dermatitis OR acne). Articles were selected when they covered at least one of the topics of interest in above-mentioned diseases. Figure 1 shows the exact flow chart of the literature search.

Measurement of treatment adherence

There is no gold standard for measuring treatment adherence. It can be very difficult to accurately quantify a patient's adherence,

which is why the number of unrecorded cases of non-adherence is probably high. Table 1 summarizes available methods for assessing treatment adherence. Traditional methods consist of patient reports, medication logs, diaries and questionnaires. These subjective methods are most commonly used among clinicians and tend to overestimate treatment adherence, as they largely rely on patients' memory and honesty.^{29–31}

Pill counts and weight-based measurements of topicals are also frequently used methods,³² especially in clinical trials. Despite the fact that these methods are practical and relatively inexpensive, they have their limitations. Pill counts do not necessarily reflect pills actually taken by the patient, one example being untaken pills discarded prior to the physician-visit.³³ Pharmacy refill records can provide information on primary treatment adherence, but do not deliver information on day-to-day adherence.³⁴

A further method used to measure treatment adherence relies on drug level assays using chemical and biological markers. These markers may be susceptible to misinterpretation. As it has been demonstrated that treatment adherence increases in the last few days before a scheduled physician-visit,³⁵ valid drug concentration on the day of the visit should not unconditionally be considered as a daily steady-state drug concentration.² Interindividual variations in drug metabolism may also influence this type of adherence measurement. Furthermore, for dermatologic treatments which often include topical agents, adherence is not routinely measurable by blood tests.

In the last decade, electronic monitoring devices have become more and more popular and claim to be a more precise and reliable method for measuring treatment adherence. Medication Event Monitoring Systems (MEMS) look like standard medication bottles, but have microprocessors in their caps which record the date and time at which they are opened.^{8,36,37} MEMS can also be utilized for monitoring topical therapy.³¹ In an 8-week psoriasis clinical trial, patients were told they would be monitored using diaries. In reality, adherence was also assessed with electronic monitors. Adherence was approximately 55% when determined by electronic monitors and 90% when determined by self-reported diaries.³⁸ This strongly suggests that traditional adherence measurements significantly overestimate patient adherence.³⁸ Drawbacks of the MEMS are the high production costs and the fact that they are not reusable.^{37,39} Moreover, opening a bottle does not necessarily proof the consumption of the medication under study.

Factors influencing treatment adherence

Treatment adherence is multidimensional and affected by the interplay of factors that can be grouped into four categories: patient-related, treatment-related, disease-related and physician-related. Table 2 gives an overview of relevant factors that influence treatment adherence. Figure 2 shows the settings of optimal treatment adherence.

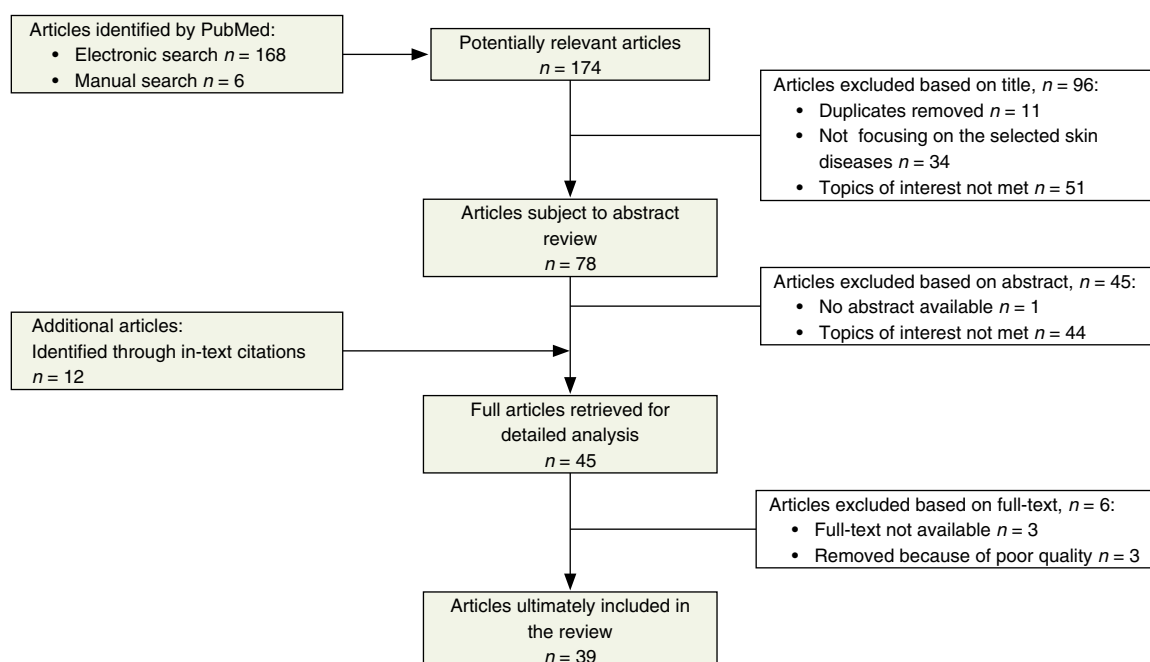


Figure 1 Flow chart of the paper selection process. *n*, number of articles.

Table 1 Methods of measuring treatment adherence

Subjective methods	Semi-objective methods	Objective methods
Patient reports and diaries	Pill counting and tube weight measurements	Drug level assays
Patient questionnaires	Pharmacy refill records	Medication Event Monitoring Systems (MEMS)
Medication logs		

MEMS, Medication Event Monitoring Systems.

Patient-related

Patient-related factors are of demographic, socioeconomic and psychological nature. Higher adherence was observed in patients who were married, employed, educated and did not smoke or drink.^{9,40,41} Age and gender also influence patient adherence, with very young or old male patients being more likely to show poor treatment adherence.^{15,40–42} Non-adherence in children and elderly patients could possibly be associated with a lack of autonomy, understanding or memory. Social support by family members, friends or support groups is associated with higher adherence rates.¹⁴ Treatment adherence declines in the presence of circumstantial barriers including distance to the clinic and physical handicaps.² Higher adherence rates were observed in patients with excellent knowledge about their disease and treatment. On the other hand, misinformation or conflicting information from another physician or from the Internet can result in non-adherence.^{2,9}

Unrealistic treatment expectations, doubts about treatment necessity and the fear of side-effects are frequent causes of treatment non-adherence in chronic skin diseases.⁴³

Corticophobia is a very common phenomenon and has a significant impact on adherence. The prevalence of topical corticophobia in patients with atopic dermatitis ranges from 21% to 84%.⁴⁴ Topical corticosteroid resistance may partially be due to non-adherence because of corticophobia.⁴⁵ Self-administered questionnaires, like the TOPICOP,⁴⁶ can be helpful to assess patients affected by topical corticophobia. Its occurrence can be minimized if physicians explain the necessity and the benefits of the treatment, emphasizing the fact that topical steroids do not have systemic effects when used in the correct way.

A very important and often underestimated patient-related factor is mental health. In fact, psychiatric disorders like depression and anxiety have been demonstrated to be significant risk factors for non-adherence.^{47–49} This finding is highly relevant, as the prevalence of psychiatric illnesses among dermatological patients ranges from 25% to 43%.^{2,47}

Lastly, patients simply forget to take their medication, forget the instructions on how to take them or lack the motivation to carry on with their treatment.⁵⁰

Table 2 Factors influencing treatment adherence in chronic inflammatory skin diseases

Patient-related	Treatment-related	Disease-related	Physician-related
• Age	• Administration route (topical, oral, s.c., i.v.)	• Longevity/Chronicity	• Physician-patient-relationship
• Gender	• Dose	• Impact on QoL	• Empathy
• Marital status	• Dosing frequency	• Severity	• Communication
• Socioeconomic status	• Duration (long-term, short-term)	• Visible lesions (e.g. facial lesions)	• Patient education
• Education level	• Complexity	• Quantity of lesions	• Patient empowering
• Employment status	• Efficacy	• Involved BSA	• Setting the right goals
• Drinking patterns	• Tolerability (e.g. side-effects, cosmetic acceptability)	• Disease itself	• Trust level
• Smoking status	• Vehicle (e.g. creams, ointments, solutions)		• Time for each patient
• Social support	• Time-consumption		• Frequency of follow-up visits
• Mental health	• Previous treatment		
• Practical barriers (e.g. distance to clinic, physical handicap)	• Financial burden		
• Understanding of disease and treatment	• Interference with patient's lifestyle		
• Treatment concerns (e.g. fear of side-effects)			
• Treatment expectations			
• Awareness of treatment necessity			
• Forgetfulness			
• Health insurance			
• Concomitant medication			

BSA, body surface area; e.g., example given; i.v., intravenous; QoL, quality of life; s.c., subcutaneous.

Treatment-related

The administration route (topical, oral, subcutaneous, intravenous) is a very important treatment-related factor and has been analysed in many studies.^{34,51–55}

Topical therapies are the cornerstone of treatment in dermatology. One of their benefits is that they bring the pharmacological agent precisely to the affected area, whilst limiting systemic effects. On the other hand, their use can be time-consuming, messy, non-esthetical and difficult to apply. In a study assessing adherence to topical medication in patients with skin disease, the overall adherence was 53% in patient reports and only 6% when measured with MEMS. In average, only 35% of the prescribed doses were used and 95% of the patients were underdosed.⁵¹ Patients often consider topical products as minor, not very effective treatments and therefore do not use them regularly.

It has been shown that adherence is better for oral than for topical therapy.^{56,57} In a study analysing a newly prescribed medication in 322 patients with different dermatologic conditions, pharmacy records revealed that 86% of oral agents compared to only 65% of topical agents were filled.³⁴ In patients with acne, the adherence to oral retinoids was 57%, whereas to topical retinoids only 2%.⁵⁴

Biologic agents have shown relatively good adherence rates, ranging from 58% to 100%,^{52,58–60} which is higher than the adherence rates reported for oral therapy.⁶¹ In two trials including only psoriasis patients, ustekinumab showed the best overall adherence rate among systemic therapies studied (acitretin, methotrexate, adalimumab, etanercept, infliximab).^{62,63} Comparing the adherence rates of different anti-tumour necrosis factor alpha agents, infliximab had better results than adalimumab and etanercept.⁵⁹ These differences could rely on the fact that

infliximab is administrated intravenously and has to be given by a healthcare professional, whereas adalimumab and etanercept can be self-administrated by the patient.⁶⁴ Chan *et al.* evaluated the impact of the administration route on adherence in a trial with 106 psoriasis patients. The self-reported adherence rates were 100% for biologic therapies, 96% for oral therapy, 93% for phototherapy and 73% for topical therapy.⁵² In fact, patients often affirm that they would prefer to take a pill or get an injection, than to apply topical agents.⁹

Treatment duration, dosing frequency, regime complexity and pill burden have an impact on patient adherence.⁴¹ Pill burden is defined as the total number of pills (tablets or capsules) that a patient takes on a daily basis.^{65,66} It has been shown that a high pill burden negatively affects treatment adherence.^{66–69} The same goes for topical treatments; however, there is no established term to describe how many creams or ointments a patient applies per day. In a MEMS-controlled acne study, a once daily combination product showed better adherence rates and better efficacy than daily application of the same two pharmacological agents separately.^{8,70} A study analysing the effect of treatment duration on adherence in patients with eczema, reported an adherence to topical tacrolimus of 96% at week 1, 64% at week 3 and only 42% at week 12.⁷¹

Side-effects, like skin irritation or dryness, are common causes of non-adherence.^{41,47,50} Treatment efficacy is another very important treatment-related factor. Unrealistic treatment expectations or the ignorance of the chronicity of a disease may lead to the assumption of an ineffective treatment, which can result in non-adherence.⁵⁰

A commonly cited reason for non-adherence to dermatologic treatment is the high financial impact.⁴¹ Especially, the cost of

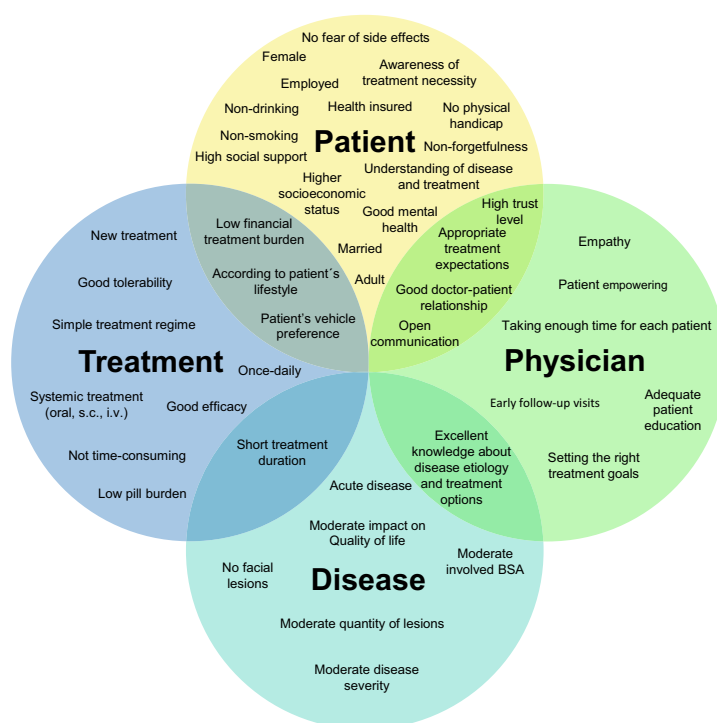


Figure 2 Settings for an optimal treatment adherence in chronic inflammatory skin disease. Figure 2 shows patient-related, treatment-related, disease-related and physician-related circumstances for an optimal treatment adherence in chronic inflammatory skin disease.

topical preparations can be very important, since these are frequently not covered by health insurance.⁷² Patients report not having filled their prescription because of cost issues and using a cream more sparsely than advised in order to postpone the payment for refills.⁷³

Disease-related

The most frequently examined disease-related factor is the chronicity of a skin disease. Patients with acute illness are much more likely to adhere to treatment than patients with chronic illness. In a prospective study with 322 patients, primary and secondary non-adherence was much higher in chronic skin diseases, such as atopic dermatitis and psoriasis, as compared to acute skin diseases like infections.³⁴

Most skin diseases have visible lesions that can cause stigmatisation and isolation, leading to a significant deterioration of the quality of life (QoL). Skin diseases with only mild impact on QoL are associated with poor adherence, whereas skin diseases with moderate reduction of QoL are associated with a better treatment adherence.^{74,75} Paradoxically, however, diseases with a severe alteration in QoL and high disease severity show the worst adherence.^{74,75} A study in psoriatic patients, examining the impact of lesion location on adherence, found a positive

correlation between facial lesions, increasing number of lesion sites, involved body surface area (BSA) and poor treatment adherence.^{41,76} Although the psychological background of these findings is poorly understood, embarrassment and shame could play an important role.

Only very few studies have examined the differences in treatment adherence between different chronic inflammatory skin diseases, especially psoriasis and atopic dermatitis. Most clinical trials have focused on one disease only.^{38,54,73,77–86} Different definitions and measurement methods for adherence make it very difficult to compare them accurately. Table 3 gives an overview of adherence rates to topical and systemic therapy in psoriasis and atopic dermatitis patients. Storm *et al.* used pharmacy records to analyse primary adherence rates in a total number of 322 patients with psoriasis, eczema and acne. Psoriasis patients showed a primary adherence of 56% and took in average 17 days to redeem their prescriptions. In eczema and acne patients, primary adherence was 70 and 91% and time to redemption was 1 and 0 days.³⁴ One study analysing adherence in chronic skin diseases, reported a tendency of patients with psoriasis, prurigo or bullous skin diseases to have the lowest adherence rates among chronic skin diseases.⁸⁷ The differences were, however, not significant.⁸⁷ Adherence to

Table 3 Adherence rates to topical and systemic therapy in psoriasis and atopic dermatitis patients

PSORIASIS					ATOPIC DERMATITIS				
References	n	Type of therapy	Measure of adherence	Adherence rate (P/S)	References	n	Type of therapy	Measure of adherence	Adherence rate (P/S)
Storm <i>et al.</i> ³⁴	86	Topical and systemic	Pharmacy refill records	Overall (P): 56%	Storm <i>et al.</i> ³⁴	137	Topical and systemic	Pharmacy refill records	Overall (P): 69%
Fouere <i>et al.</i> ⁹³	281	Topical	Self-reports	Topical (S): 27%	Torrel <i>et al.</i> ⁸⁴	309	Topical	Questionnaire	Topical (S): 65%
Feldmann <i>et al.</i> ¹⁰²	29	Topical	MEMS	Topical (S): 55%	Krejci-Manwaring <i>et al.</i> ⁸⁸	26	Topical	MEMS	Topical (S): 32%
Zaghloul and Goodfield ⁴¹	201	Topical and systemic	Self-reports	Overall (S): 60%	Wilson <i>et al.</i> ⁹⁰	20	Topical	MEMS	Topical (S): 70%
Richards <i>et al.</i> ⁴⁰	120	Topical and systemic	Questionnaire	Overall (S): 61%	Yentzer <i>et al.</i> ⁸⁶	41	Topical	MEMS	Topical (S): 50%
Altobelli <i>et al.</i> ⁸²	1689	Topical and systemic	Questionnaire	Overall (S): 46%	Hix <i>et al.</i> ⁹¹	10	Topical	Diaries MEMS	Topical (S): 100% Topical (S): 40%
Van de Kerkhof <i>et al.</i> ⁵⁵	839	Topical and systemic	Questionnaire	Topical (S): 51% Systemic (S): 97%	Krejci-Manwaring <i>et al.</i> ⁷¹	Not given	Topical and systemic	MEMS	Topical (S): 64% Systemic (S): 85%
Hambly <i>et al.</i> ⁹⁴	106	Systemic	Questionnaire	Systemic (S): 76%	Law Ping Man <i>et al.</i> ⁸⁵	56	Systemic	Questionnaire	Systemic (S): 77%
Dommasch <i>et al.</i> ⁸²	22 742	Systemic	Diaries	Systemic (S): 62%					
Clemmensen <i>et al.</i> ⁸³	71	Biologics	Self-reports	Biologics (S): 96%					
Zschocke <i>et al.</i> ⁶⁰	246	Biologics	Questionnaire	Biologics (S): 58%					
Chan <i>et al.</i> ⁵²	106	Topical and systemic	Self-reports	Overall (S): 86% Topical (S): 75% Oral (S): 96% Biologics (S): 100%					

MEMS, Medication Event Monitoring System; n, number of patients; (P), primary adherence rate; (S), secondary adherence rate.

topical agents in patients with atopic dermatitis ranged between 32% and 100%,^{53,88–91} in psoriasis patients between 27 and 75%.^{38,41,52,56,92–94} Adherence to oral prednisolone therapy in patients with moderate to severe hand dermatitis was 85%.⁷¹ Adherence to oral therapy in psoriasis patients ranged from 62% to 96%.^{52,55,62} Since only few studies with inconsistent results are published, the significance of the reported differences in adherence between chronic inflammatory skin diseases remains unclear. However, there is a tendency towards better adherence in atopic dermatitis patients compared to psoriasis patients. This topic needs to be further analysed in future studies, in order to define which patients should most closely be monitored for treatment adherence.

Physician-related

A paternalistic relationship between physician and patient does not usually promote treatment adherence.¹⁹ On the contrary, patients should be considered as independent partners with the goal of reaching mutual agreement. When patients feel included in the decision-making process of their treatment, they are more likely to adhere to it.^{9,12} Open communication and empathy are the cornerstones of a good physician-patient relationship. Physicians need to develop reliable teaching skills, in order to properly educate their patients about the disease and the recommended treatment.^{1,95} In this context it is very important not to use a medical terminology, but to adapt to patients' vocabulary. Inadequate assumptions about patients' baseline level of knowledge can lead to misunderstandings and are common causes of non-adherence.² In particular, for patients with chronic skin diseases, it is very important to set the right treatment goals, namely controlling symptoms, rather than healing the disease.⁸¹ Furthermore, it is very important to take enough time to listen to patients' needs and concerns. In fact, the trust level of a patient in his physician is a significant predictor for treatment adherence.⁹⁶ Thom *et al.* prospectively analysed the association between patients' trust in their physician and adherence to treatment. In the highest trust category, 62% of patients followed their physicians' recommendations, compared to 14% in the lowest trust category.⁹⁶

Strategies to improve treatment adherence

Since non-adherence can lead to treatment failure, it is crucial to elaborate strategies to improve adherence. Because there is no single solution that works for every patient, the best approach may be to combine several strategies. Figure 3 summarizes different strategies to optimize treatment adherence.

Reminder programs using e-mails, phone calls, text messages or smartphone applications can be helpful to counteract patients' forgetfulness.⁹⁷ The success rate of these programs in improving adherence is, however, inconsistent according to the

literature, and depends on patients' character and personality.^{16,56,98,99}

Simplifying treatment regimes and reducing pill burden are easy methods to enhance treatment adherence. Once-daily regimes with combined pharmacological agents are preferable, since they are more manageable for the patient. The treatment should be tolerable and individually tailored to each patient's lifestyle. Especially for topical treatments, physicians should select vehicles according to patients' personal preferences.^{97,100} A survey study of 120 patients with psoriasis showed that patients preferred creams to ointments,⁴⁰ probably because they are less messy and take less time to be absorbed. The affected body area also plays an important role when choosing the right vehicle for a topical agent. For example, foams and solutions are more suitable for application to the scalp than creams and ointments.¹⁰¹

Physicians should also be conscious about the financial burden of their prescriptions and should consider providing generics, if equally effective. There is no better way to ensure that a patient will not take his medication than prescribing a too expensive medication, which is not reimbursed.

Since oral, subcutaneous and intravenous therapy are associated with better adherence rates than topical therapy,⁵⁷ physicians should weigh the risks of a more invasive treatment against the risks of non-response to treatment due to non-adherence.⁴⁹

Scheduling early follow-up visits has also proven to increase treatment adherence, according to what Feinstein calls 'the white-coat-compliance'.^{35,102} Especially, in the early stages of a treatment, additional visits can be helpful to establish a solid

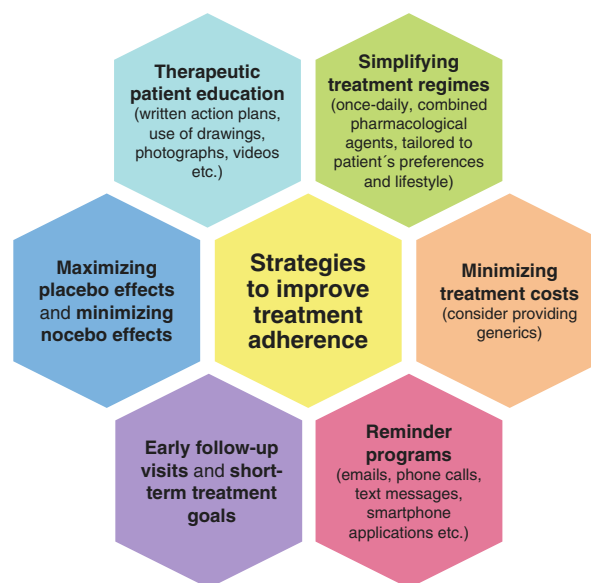


Figure 3 Strategies to improve treatment adherence.

treatment routine and could possibly result in fewer overall-visits.¹⁶ In a study evaluating patients with psoriasis, atopic dermatitis and hand dermatitis, optimal adherence was found 2 days before and 2 days after a physician-visit.⁵¹ Furthermore, additional visits give the physician the opportunity to discuss potential questions with the patient, evaluate treatment efficacy and closely monitor side-effects. In some countries insurance issues limit the ability of physicians to frequently control their patients. The above measures can, however, help to build a strong bond with the patient and to reinforce his feeling of safety.^{38,88} Short-term treatment goals can seem less oppressive and more realistically achievable, which is why it is recommendable to set new goals after each visit.

Adequate patient education plays a key role in ensuring optimal treatment adherence. In fact, helping the patient to understand his disease can empower and motivate him to take responsibility for treatment outcome. Therapeutic patient education (TPE)¹⁰³ has been shown to increase treatment adherence and outcome in chronic inflammatory skin disease.^{15,104–106} In a randomized controlled multicentre study, Heratizadeh *et al.*¹⁰⁷ showed that adult patients with atopic dermatitis educated in a 12-h multidisciplinary training programme including dermatological, nutritional and psychological aspects had a significant improvement in their coping behaviour, QoL and disease severity after 1 year of follow-up. Similarly, Reich *et al.*^{108,109} developed the Topical Treatment Optimization Programme (TTOP), an educational and supportive intervention for psoriasis patients. In a 64-week clinical trial with 1790 psoriasis patients, a significantly better clinical outcome was reported in patients randomized to TTOP as compared to standard care.¹⁰⁸ In paediatric and elderly patients, TPE should include both parents and caregivers. Moreover, TPE in small patient groups has been shown to maximize educational benefits and encourage exchange of knowledge and experiences.¹⁰⁷ In this context, the use of drawings, photographs and videos can be helpful.⁹ Written action plans can also be beneficial to address forgetfulness and emphasize the treatment details.¹¹⁰ Especially, for topical therapy, inexact dosing instructions should be avoided since they leave too much room for individual interpretation.

Another way of promoting patient adherence is to maximize placebo and minimize nocebo effects. Placebo and nocebo effects describe positive and negative treatment effects that rely exclusively on patients' expectations and beliefs about treatment outcome.¹¹¹ For example, physician's emphasis on the effectiveness of a treatment can improve its outcome.¹¹² On the contrary, emphasis on possible side-effects can result in a nocebo effect and significantly decrease the outcome.¹¹³ A meta-analysis investigated the magnitude of the placebo effect on itch in patients with psoriasis, atopic dermatitis and urticaria. Patients were told that they would get a potent antipruriginous drug. Even in patients blindly randomized to placebo, itch significantly reduced by 24%.¹¹⁴ Physicians should systematically make use of

placebo effects and wherever possible consciously avoid nocebo effects, but without withholding important safety information, in order to maximize treatment adherence and consequently efficacy.

Last but not least, the importance of open and explicit patient-information concerning treatment adherence should not be underestimated. Patients are often not aware of their poor adherence and its consequences, and ignore means to improve it.

Outlook and conclusion

Treatment adherence is key for treatment outcome, especially in dermatology. Nevertheless, the significance of adherence and the need to focus on adherence research has only recently been realized.

New technologies are currently available for more accurate measurement of treatment adherence. Despite this, the majority of clinical trials in dermatology are still based on subjective methods such as medication logs and weights measurements. It can be assumed that non-adherence rates are higher than recorded, jeopardizing the reported treatment efficacy rates. This implies that much larger sample sizes are required in trials to achieve statistical significance.¹¹⁵ Another limitation of most studies on adherence in dermatology is the absence of differentiation between the distinct phases of treatment adherence, as usually only an overall adherence rate is reported.¹⁶ Specification of which adherence phase is being analysed is needed, and could address the fulfilment of the prescription, the dosage, the frequency of dosing, or the treatment duration. The literature lacks qualitative studies on treatment adherence, in particular in dermatology. Implementing objective measurements of adherence like MEMS and specifying the precise phases of treatment adherence considered would add value to future clinical trial publications.

While there is so much effort and funding going into the development of new drugs, it is equally important to improve the adherence to drugs that are already on the market, in order for them to reach their full therapeutic potential. Understanding the complex causes of non-adherence in the dermatologic patient creates opportunities to improve adherence in the future. This would not only benefit our patients because of better treatment outcomes, but would also represent an extraordinary reduction of healthcare costs.

This review showed that physicians should, in order to maximize treatment adherence, take enough time for their patients and listen to their patient's needs and concerns. However, this constitutes a major challenge in times of increasing economic pressure on the medical system, which forces physicians to increase their patient turnover. Furthermore, current physician financing systems remunerate interventional procedures better than time taken to speak with a patient.

It is also important to bear in mind that patients vary in their willingness and ability to adhere to a treatment. Poor adherence

frequently comprises drug omissions and drug holidays.¹¹⁶ Besides improving adherence, the use of 'forgiving pharmaceuticals'³⁷ could be another possibility to increase treatment outcome in selected patients. 'Forgiving pharmaceuticals' are drugs with long duration of action, providing solid steady-state drug concentrations. They are therefore less affected by missed dosages and intermittent dosing patterns. A downside of these long-acting drugs is that they may be more susceptible for overdosing and adverse events.^{37,117}

Finally, in order to progress, continuous efforts need to be made to raise awareness about the high prevalence, causes and consequences of poor treatment adherence. Absolute adherence to treatment may not be realistically achievable, but we should emphasize on its importance in order to maximize adherence as far as possible.

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