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

L. Eicher,1 M. Knop,2 N. Aszodi,1 S. Senner,1 L.E. French,1,2 A. Wollenberg1,2,*
1Klinik und Poliklinik für Dermatologie und Allergologie, Klinikum der Universität München, Munich, Germany
2Derma I, München Klinik, Munich, Germany
*Correspondence: A. Wollenberg. E-mail: wollenberg@lrz.uni-muenchen.de

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.

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.26

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.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’.19,20 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.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.
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%.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 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.
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)      | • Perception                                          |                                                      |                                                       |
| • Treatment expectations                              | • Awareness                                           |                                                      |                                                       |
| • Awareness of treatment necessity                    | • Forgettingness                                       |                                                      |                                                       |
| • Forgetfulness                                       | • Health insurance                                     |                                                      |                                                       |
| • Concomitant medication                              | • 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. 56–69 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. 5,70 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...
topical preparations can be very important, since these are frequently not covered by health insurance. 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.

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.

Most skin diseases have visible lesions that can cause stigmatization 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. Paradoxically, however, diseases with a severe alteration in QoL and high disease severity show the worst adherence. 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. 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. 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. 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.
| References         | n  | Type of therapy                  | Measure of adherence | Adherence rate (P/S) | Adherence rate (P/S) |
|--------------------|----|----------------------------------|----------------------|----------------------|----------------------|
| Storm et al.       | 86 | Topical and systemic             | Pharmacy refill records | Overall (P): 56% | Storm et al.         | 137 | Topical and systemic | Pharmacy refill records | Overall (P): 69% |
| Fouere et al.      | 281| Topical                          | Self-reports          | Topical (S): 27%    | Torrelo et al.       | 309 | Topical              | Questionnaire          | Topical (S): 65% |
| Feldmann et al.    | 29 | Topical                          | MEMS                  | Topical (S): 55%    | Krejci-Manwaring et al. | 26 | Topical              | MEMS                  | Topical (S): 32% |
| Zaghioui and       | 201| Topical and systemic             | Self-reports          | Overall (S): 60%    | Wilson et al.        | 20  | Topical              | MEMS                  | Topical (S): 70% |
| Goodfield          |    |                                  |                       |                      |                      |
| Richards et al.    | 120| Topical and systemic             | Questionnaire         | Overall (S): 61%    | Yentzer et al.       | 41  | Topical              | MEMS                  | Topical (S): 50% |
| Allobelli et al.   | 1689| Topical and systemic            | Questionnaire         | Overall (S): 46%    | Hix et al.           | 10  | Topical              | Diaries               | Topical (S): 100% |
| Van de Kerkhof et al | 839 | Topical and systemic           | Questionnaire         | Topical (S): 51%; Systemic (S): 97% | Krejci-Manwaring et al. | 71 | Not given             | MEMS                  | Topical (S): 64%; Systemic (S): 85% |
| Hambly et al.      | 106| Systemic                        | Questionnaire         | Systemic (S): 76%   | Law Ping Man et al.  | 56  | Systemic             | Questionnaire         | Systemic (S): 77% |
| Dommasch et al.    | 742| Systemic                        | Diaries               | Systemic (S): 62%   |                      |     |                      |                       |                      |
| Clemmensen et al.  | 71 | Biologics                        | Self-reports          | Biologics (S): 96%  |                      |     |                      |                       |                      |
| Zschokie et al.    | 246| Biologics                        | Questionnaire         | Biologics (S): 58%  |                      |     |                      |                       |                      |
| Chan et al.        | 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.14 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.87 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.19

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
treatment routine and could possibly result in fewer overall-visits. 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. 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.

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) has been shown to increase treatment adherence and outcome in chronic inflammatory skin disease. In a randomized controlled multicentre study, Heratizadeh et al. 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. 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. 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. In this context, the use of drawings, photographs and videos can be helpful. Written action plans can also be beneficial to address forgetfulness and emphasize the treatment details. 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. For example, physician’s emphasis on the effectiveness of a treatment can improve its outcome. On the contrary, emphasis on possible side-effects can result in a nocebo effect and significantly decrease the outcome. 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%. 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. 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. 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.\textsuperscript{116} Besides improving adherence, the use of ‘forgiving pharmaceuticals’\textsuperscript{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.\textsuperscript{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.

References
1 Adherence to long-term therapies: evidence for action, 2003; URL: https://www.who.int/chp/knowledge/publications/adherence_report/en/ (last accessed: 4 April 2019).
2 Hodari KT, Nanton JR, Carroll CL, Feldman SR, Balkrishnan R. Adherence in dermatology: a review of the last 20 years. J Dermatol Treat 2006; 17: 136–142.
3 Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. Pharmacoepidemiol Drug Saf 2006; 15: 565–574; discussion 575–567.
4 Hearnshaw H, Lindemeyer A. What do we mean by adherence to treatment and advice for living with diabetes? A review of the literature on definitions and measurements. Diabet Med 2006; 23: 720–728.
5 Vrijens B, de Geest S, Hughes DA et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 2012; 73: 691–705.
6 Krueger KP, Berger BA, Felkey B. Medication adherence and persistence: a comprehensive review. Adv Ther 2005; 22: 313–356.
7 Sawyer SM, Aroni RA. Sticky issue of adherence. J Paediatr Child Health 2001; 37: 2–5.
8 Ahn CS, Culp L, Huang WW, Davis SA, Feldman SR. Adherence in dermatology. J Dermatol Treat 2017; 28: 94–103.
9 Peirowski JA. Compliance: the dermatologic patient. Int J Dermatol 1998; 27: 608–611.
10 Dunbar J. Adherence to medical advice: a review. Int J Mental Health 1980; 9: 70–87.
11 Luftey KE, Wishner WJ. Beyond “compliance” is “adherence”. Improving the prospect of diabetes care. Diabetes Care 1999; 22: 635–639.
12 Taube KM. Patient–doctor relationship in dermatology: from compliance to concordance. Acta Derm Venereol 2016; 96: 25–29.
13 McKay CD, Verhagen E. ‘Compliance’ versus ‘adherence’ in sport injury prevention: why definition matters. Br J Sports Med 2016; 50: 382–383.
14 Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. J Clin Pharm Ther 2001; 26: 331–342.
15 Cork MJ, Britton J, Butler L, Young S, Murphy R, Keohane SG. Comparison of parent knowledge, therapy utilization and severity of atopic eczema before and after explanation and demonstration of topical therapies by a specialist dermatology nurse. Br J Dermatol 2003; 149: 582–589.
16 Feldman SR, Vrijens B, Gieler U, Piaserico S, Puig L, van de Kerkhof P. Treatment adherence intervention studies in dermatology and guidance on how to support adherence. Am J Clin Dermatol 2017; 18: 253–271.
17 Thinking outside the pillbox: a system-wide approach to improving patient medication adherence for chronic disease, 2009. URL: https://www.nehi.net/writable/publication_files/file/pa_issue_brief_final.pdf (last accessed: 4 April 2019).
18 Targeting adherence. Improving patient outcomes in Europe through community pharmacists’ intervention, 2008. URL: www.pgeu.eu/en/policy/5-adherence.html (last accessed: 4 April 2019).
19 Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005; 353: 487–497.
20 Mekler K, Hage A. Drugs don’t work in patients who don’t take them. Z Kinder Jugendpsychiatr Psychother 2019: 1–5.
21 Brown MT, Bussell JK. Medication adherence: WHO cares? Mayo Clin Proc 2011; 86: 304–314.
22 Urquhart J. Pharmacoeconomic consequences of variable patient compliance with prescribed drug regimes. Pharmacoconomics 1999; 15: 217–228.
23 Murphy J, Coster G. Issues in patient compliance. Drugs 1997; 54: 797–800.
24 McKenney JM, Munrow WP, Wright JT Jr. Impact of an electronic medication compliance aid on long-term blood pressure control. J Clin Pharmacol 1992; 32: 277–283.
25 Dunbar-Jacob J, Dewey E. Compliance with antihypertensive regimen: a review of the research in the 1980s. Ann Behav Med 1991; 13: 31–39.
26 Kogut SJ, Andrade SE, Willey C, Larrat EP. Nonadherence as a predictor of antidiabetic drug therapy intensification (augmentation). Pharmacoeconom Drug Saf 2004; 13: 591–598.
27 Cranker J, Vachon L, Desforges C, Sussman NM. Dose frequency and dose interval compliance with multiple antiepileptic medications during a controlled clinical trial. Epilepsia 1995; 36: 1111–1117.
28 Paterson DL, Swindells S, Mohr J et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000; 133: 21–30.
29 Moriski DE, Ang A, Krousel-Wood M, Ward HF. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich) 2008; 10: 348–354.
30 Pawin H, Beylot C, Chivot M et al. Creation of a tool to assess adherence to treatments for acne. Dermatology 2009; 218: 26–32.
31 Balkrishnan R, Carroll CL, Camacho FT, Feldman SR. Electronic monitoring of medication adherence in skin disease: results of a pilot study. J Am Acad Dermatol 2003; 49: 651–654.
32 Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD, Mukherjee J. Can simple clinical measurements detect patient noncompliance? Hypertension 1980; 2: 757–764.
33 Roth HP, Caron HS. Accuracy of doctors’ estimates and patients’ statements on adherence to a drug regimen. Clin Pharmacol Ther 1978; 23: 361–370.
34 Storm A, Andersen SE, Benfeldt E, Serup J. One in 3 prescriptions are never redeemed: primary nonadherence in an outpatient clinic. J Am Acad Dermatol 2008; 59: 27–33.
35 Feinstein AR. On white-coat effects and the electronic monitoring of compliance. Arch Intern Med 1990; 150: 1377–1378.
36 Urquhart J. The electronic medication event monitor. Lessons for pharmacotherapy. Clin Pharmacokinet 1997; 32: 345–356.
37 Koehler AM, Maibach HI. Electronic monitoring in medication adherence measurement. Implications for dermatology. Am J Clin Dermatol 2001; 2: 7–12.
38 Carroll CL, Feldman SR, Camacho FT, Manuel JC, Balkrishnan R. Adherence to topical therapy decreases during the course of an 8-week psoriasis clinical trial: commonly used methods of measuring adherence to topical therapy overestimate actual use. J Am Acad Dermatol 2004; 51: 212–216.
39 Rosen MI, Rigby MO, Salahi JT, Ryan CE, Cramer JA. Electronic monitoring and counseling to improve medication adherence. Behav Res Ther 2004; 42: 409–422.
Patients with psoriasis and their compliance with medication. J Am Acad Dermatol 1999; 41: 546–549.

Moret L, Anthoine E, Aubert-Waistaux H et al. TOPICOP(c): a new scale evaluating topical corticosteroid phobia among atopic dermatitis outpatients and their parents. PLoS ONE 2013; 8: e76493.

Renzi C, Picardi A, Abeni D et al. Association of dissatisfaction with care and psychiatric morbidity with poor treatment compliance. Arch Dermatol 2002; 138: 337–342.

Picardi A, Abeni D, Melchi CF, Puddu P, Pasquinii P. Psychiatric morbidity in dermatological outpatients: an issue to be recognized. Br J Dermatol 2000; 143: 983–991.

Gupta G, Mallefet P, Kress DW, Sergeant A. Adherence to topical dermatological therapy: lessons from oral drug treatment. Br J Dermatol 2009; 161: 221–227.

Brown KK, Rehmus WE, Kimball AB. Determining the relative importance of physician-patient interaction and communication. J Am Acad Dermatol 2001; 45: 1279–1310.

Sabbatini M, Garofalo G, Borrelli S et al. Effect of a reduced pill burden on therapeutic adherence to calcineurin inhibitors in renal transplant recipients: an observational study. Patient Prefer Adherence 2014; 8: 73–81.

Sutton SS, Al-Dabagh A, Davis SA. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001; 23: 1296–1310.

Yentzer BA, Ade RA, Fountain JM et al. Simplifying regimens promotes greater adherence and outcomes with topical acne medications: a randomized controlled trial. Cutis 2010; 86: 103–108.

Krejci-Manwaring J, McCarty MA, Camacho F et al. Adherence with topical treatment is poor compared with adherence with oral agents: implications for effective clinical use of topical agents. J Am Acad Dermatol 2006; 54: S235–S236.

Zeber JE, Grazier KL, Valenstein M, Blow FC, Lantz PM. Effect of a medication copayment increase in veterans with schizophrenia. Am J Manag Care 2007; 13: 335–346.

Richards HL, Fortune DG, Griffiths CE. Adherence to treatment in patients with psoriasis. J Eur Acad Dermatol Venereol 2006; 20: 370–379.

Wolkenstein P, Consoli S, Roujeau J, Greb J. La relation médicament-maladie. L’annonce d’une maladie grave. La formation du patient atteint de maladie chronique. La personnalisation de la prise en charge médicale. Ann Dermatol Venereol 2001; 128: 9–12.

Consoli S. Consoli S. Dermatologie. Est si C’était Votre Patient? Clés de Communication Médecin-patient. 15 Situations Concrètes. Editions Scientifiques L&C, Paris, France. 2005. ISBN 2-914275-64-1.

Negro G, Angelini G, Grosso SB, Gaula G, Sategna-Guidetti C. Psychiatric predictors of noncompliance in inflammatory bowel disease: psychiatry and compliance. J Clin Gastroenterol 2001; 32: 66–68.

Pitel N, Feldman SR. Adherence in atopic dermatitis. Adv Exp Med Biol 2017; 1027: 139–159.

Snyder A, Farhangian M, Feldman SR. A review of patient adherence to topical therapies for treatment of atopic dermatitis. Cutis 2015; 96: 397–401.

Stein Gold LF. Topical therapies for psoriasis: improving management strategies and patient adherence. Semin Cutan Med Surg 2016; 35: S36–S44; quiz S45.

Alinia H, Moradi Tuchayi S, Smith JA et al. Long-term adherence to topical psoriasis treatment can be abysmal: a 1-year randomized intervention study using objective electronic adherence monitoring. Br J Dermatol 2017; 176: 759–764.

Fischer G. Compliance problems in paediatric atopic eczema. Australas J Dermatol 1996; 37(Suppl 1): S10–S13.

Altobelli E, Marzilliano C, Fargnoli MC et al. Current psoriasis treatments in an Italian population and their association with socio-

Intentional and unintentional medication non-adherence in psoriasis: the role of patients’ medication beliefs and habit strength. J Invest Dermatol 2018; 138: 785–794.

Dommasch ED, Lee MP, Joyce CJ, Garry EM, Gagne JJ. Drug utilization patterns and adherence in patients on systemic medications for the treatment of psoriasis: a retrospective, comparative cohort study. J Am Acad Dermatol 2018; 79: 1061–1068.e1061.

Ross C, Marshman G, Grillo M, Stanford T. Biological therapies for psoriasis: adherence and outcome analysis from a clinical perspective. Australas J Dermatol 2016; 57: 137–140.

Schwartzman S, Morgan GJ Jr. Does route of administration affect the outcome of TNF antagonist therapy? Arthritis Res Ther 2004; 6(Suppl 2): S19–S23.

Polypharmacy. URL https://en.wikipedia.org/wiki/Polypharmacy (last accessed: 4 April 2019).

Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. J Am Acad Dermatol 2014; 69: 138–140.
demographical and clinical features. J Eur Acad Dermatol Venereol 2012; 26: 976–982.

83 Clemmensen A, Spon M, Skov L, Zachariae C, Gniadecki R. Responses to ustekinumab in the anti-TNF agent-naive vs. anti-TNF agent-exposed patients with psoriasis vulgaris. J Eur Acad Dermatol Venereol 2011; 25: 1037–1040.

84 Torrelo A, Ortiz J, Alomar A, Ros S, Pedrosa E, Cuervo J. Health-related quality of life, patient satisfaction, and adherence to treatment in patients with moderate or severe atopic dermatitis on maintenance therapy: the CONDA-SAT study. Acta Dermofatolivitis 2013; 104: 409–417.

85 Law Ping Man S, Bouzille G, Beneton N, Safa G, Dupuy A, Droitcourt C. Drug survival and postdrug survival of first-line immunosuppressive treatments for atopic dermatitis: comparison between methotrexate and ciclosporine. J Eur Acad Dermatol Venereol 2018; 32: 1327–1335.

86 Yentzer BA, Camacho FT, Young T, Fountain JM, Clark AR, Feldman SR. Good adherence and early efficacy using desonide hydrogel for atopic dermatitis: results from a program addressing patient compliance. J Drugs Dermatol 2010; 9: 324–329.

87 Amraoui N, Galloju S, Berraho MA, Najjari C, Mernissi FZ. Adherence to treatment in chronic dermatoma: about 200 cases. Pan Afr Med J 2015; 22: 116.

88 Krejci-Manwaring J, Tusa MG, Carroll C et al. Stealth monitoring of adherence to topical medication: adherence is very poor in children with atopic dermatitis. J Am Acad Dermatol 2007; 56: 211–216.

89 Yentzer BA, Ade RA, Fountain JM et al. Improvement in treatment adherence with a 3-day course of fluocinonide cream 0.1% for atopic dermatitis. Cutis 2010; 86: 208–213.

90 Wilson R, Camacho F, Clark AR et al. Adherence to topical hydrocortisone 17-butyrate 0.1% in different vehicles in adults with atopic dermatitis. J Am Acad Dermatol 2009; 60: 166–168.

91 Hix E, Gustafson CJ, O’Neill JL et al. Adherence to a five day treatment course of topical fluocinonide 0.1% cream in atopic dermatitis. Dermatol Online J 2013; 19: 2009.

92 Belinconh I, Rivera R, Blanch C, Cornellas M, Lizin L. Adherence, satisfaction, and preferences for treatment in patients with psoriasis in the European Union: a systematic review of the literature. Patient Prefer Adherence 2016; 10: 2557–2567.

93 Fouere S, Adjaji L, Pawin H. How patients experience psoriatic results from a European survey. J Eur Acad Dermatol Venereol 2005; 19(Suppl 3): 2–6.

94 Hamblly R, Kelly A, Gilhooley E et al. Medication adherence among patients with psoriasis on traditional systemic and biologics treatment. Br J Dermatol 2018; 178: e66–e68.

95 Griffiths S. A review of the factors associated with patient compliance and the taking of prescribed medicines. Br J Gen Pract 1990; 40: 114–116.

96 Thom DH, Ribbil KM, Stewart AL, Luke DA. Further validation and reliability testing of the Trust in Physician Scale. The Stanford Trust Study Physicians. Med Care 1999; 37: 510–517.

97 Zschocke I, Mrowietz U, Karakasili E, Reich K. Non-adherence and measures to improve adherence in the topical treatment of psoriasis. J Eur Acad Dermatol Venereol 2014; 28(Suppl 2): 4–9.

98 Svendsen MT, Andersen F, Andersen KH et al. A smartphone application supporting patients with psoriasis improves adherence to topical treatment: a randomized controlled trial. Br J Dermatol 2018; 179: 1062–1071.

99 Svendsen MT, Andersen F, Andersen KH, Andersen KE. Can an app supporting psoriasis patients improve adherence to topical treatment? A single-blind randomized controlled trial. BMC Dermatol 2018; 18: 2.

100 Jackson IM, Pelle M. Topical rosacea therapy: the importance of vehicles for efficacy, tolerability and compliance. J Drugs Dermatol 2011; 10: 627–633.

101 Feldman SR, Housman TS. Patients’ vehicle preference for corticosteroid treatments of scalp psoriasis. Am J Clin Dermatol 2003; 4: 221–224.

102 Feldman SR, Camacho FT, Krejci-Manwaring J, Carroll CL, Balkrishnan R. Adherence to topical therapy increases around the time of office visits. J Am Acad Dermatol 2007; 57: 81–83.

103 Staller JF, Bernier C, Ball A et al. Therapeutic patient education in atopic dermatitis: worldwide experiences. Pediatr Dermatol 2013; 30: 329–334.

104 Liang Y, Tian J, Shen CP et al. Therapeutic patient education in children with moderate to severe atopic dermatitis: a multicenter randomized controlled trial in China. Pediatr Dermatol 2018; 35: 70–75.

105 Caldarola G, De Simone C, Moretta G, Prescia A, Peris K. Role of personalized medication training in improving efficacy and adherence to a topical therapy in psoriatic patients. J Dermatolog Treat 2017; 28: 722–725.

106 Reich K, Mrowietz U, Karakasili E, Zschocke I. Development of an adherence-counselling program supporting patients with psoriasis improve adherence to topical treatment? A single-blind randomized controlled trial. Br J Dermatol 2017; 177: 197–205.

107 Caldarola G, De Simone C, Moretta G, Prescia A, Peris K. Role of personalized medication training in improving efficacy and adherence to a topical therapy in psoriatic patients. J Dermatolog Treat 2017; 28: 722–725.

108 Reich K, Mrowietz U, Karakasili E, Zschocke I. Development of an adherence-enhancing intervention in topical treatment termed the topical treatment optimization program (TTOP). Arch Dermatol Res 2014; 306: 667–676.

109 Reich K, Zschocke I, Bachelez H et al. A Topical Treatment Optimization Programme (TTOP) improves clinical outcome for calcipotriol/betamethasone gel in psoriasis: results of a 6-week multinational randomized phase IV study in 1790 patients (PSO-TOP). Br J Dermatol 2017; 179: 698–700.

110 Evers AW. Using the placebo effect: how expectations and learned immune function can optimize dermatological treatments. Exp Dermatol 2017; 26: 18–21.

111 van Laarhoven AIM, van der Sman-Mauriks IM, Donders ART, Pronk MC, van de Kerkhof PCM, Evers AW. Placebo effects on itch: a meta-analysis of clinical trials of patients with dermatological conditions. J Invest Dermatol 2015; 135: 1234–1243.

112 Steinkopf L. Enhancing drug compliance and the placebo effect by raising subjective expectations. Med Hypotheses 2012; 79: 698–700.

113 Evers AW. Using the placebo effect: how expectations and learned immune function can optimize dermatological treatments. Exp Dermatol 2017; 26: 18–21.

114 van Laarhoven AIM, van der Sman-Mauriks IM, Donders ART, Pronk MC, van de Kerkhof PCM, Evers AW. Placebo effects on itch: a meta-analysis of clinical trials of patients with dermatological conditions. J Invest Dermatol 2015; 135: 1234–1243.

115 Goldsmith CH. The effect of compliance distributions on therapeutic trials. In: Haynes RB, Taylor DW, Sackett DL, eds. Compliance in Health. Elsevier, London, 2004.

116 Urquhart J. Role of patient compliance in clinical pharmacokinetics. A review of recent research. Clin Pharmacokinet 1994; 27: 202–215.

117 Meredith PA. Therapeutic implications of drug ‘holidays’. Eur Heart J 1996; 17(Suppl A): 21–24.