Medical adherence to topical corticosteroid preparations prescribed for psoriasis: A systematic review

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ABSTRACT

Objective: Topical corticosteroids and corticosteroid combinations are the principal treatments in psoriasis. The aim of this study was to investigate published literature dealing with medical adherence to topical corticosteroid or corticosteroid combinations in patients with psoriasis.

Materials and methods: Systematic electronic searches in English language literature were done until September 2015 without publication date restriction.

Results: We identified 11 studies consisting of five surveys, two prospective studies, one qualitative study, one mixed-method study, one register study, and one interventional study. Observation periods varied and rates of nonadherence ranged from 8% to 88.3%. The rates were reported by patients on eight nonvalidated scales and one validated scale, measured by medication weight in two studies, and in two studies rates of nonadherence were measured using prescription registers. Thirty-four multifactorial determinants of nonadherence were found. One designed intervention consisted of a disease management program, which improved adherence in the study period. Overall, the studies included were heterogeneous in design and had a high risk of bias.

Conclusion: To improve health outcome in topical treatment of psoriasis, further studies should be conducted addressing determinants of nonadherence and test interventions to improve adherence. Validated measurements of medical nonadherence, prescription registers, or medication-weight are needed.

Introduction

Psoriasis affects about 2–4% of the population in the Western world (1). Prescribed topical corticosteroids and corticosteroid combinations constitute the first-line topical treatment of psoriasis and are considered safe and effective, when used as prescribed (2,3). Psoriasis is a disease with multi-organ involvement and has been associated with obesity (4), metabolic syndrome (5), cardiovascular disease, and diabetes (6–8). Yet, apart from methotrexate, no antipsoriatic treatment has proven effective on reducing associated comorbidities (9). Psoriasis negatively affects quality of life (10), is a socio-economic burden for the patients (11,12), and satisfaction with used treatments is low (13,14). For a satisfactory treatment outcome, correct application of medication is necessary, but Storm et al. found that one in three prescriptions is never picked up at the pharmacy (15). According to Urquhart et al. (16), a failure to treatment can be due to nonadherence, nonabsorption, or nonresponse.

“Drugs don’t work in patients who don’t take them”, C. Everett Koop (17).

This sentence describes a complex scientific field; the study of medical adherence. Vrijens et al. (18) defined medical adherence as “the process by which patients take their medication as prescribed”. Nonadherence should be distinguished as intentional (patients make a deliberate decision to not adhere) and unintentional (nonadherence is due to unforeseen barriers, such as forgetting). This is important, since factors influencing intentional and unintentional nonadherence are likely to be different. Nonadherence is divided into primary (not collecting the prescribed medication) and secondary (specific medication-taking behaviors such as late initiation of prescribed treatments, suboptimal implementation of dosing regimens, or early discontinuation). The time between initiation and discontinuation is termed persistence, as illustrated in Figure 1. Secondary medication nonadherence is often defined as taking less than 80% of the prescribed medication (19), but no consensus exists. Medical nonadherence in chronic diseases is high (20) and determinants of nonadherence are multifaceted (21).

A Cochrane review from 2014 addressed interventions designed to improve medical adherence. The review found adherence studies heterogeneous regarding the large differences between published studies in terms of medical condition, patient population, intervention, measures of adherence, and clinical outcomes. This heterogeneity has the consequence that it is inappropriate to pool results in a metanalyses (19). In addition, adherence rates in clinical trials tend to be higher than in real-life settings (22).

Previous systematic reviews addressing medical adherence in topically treated psoriasis have focused on overall topical treatments (23,24). Since topically prescribed corticosteroids and corticosteroid combinations are the first-line treatments that the physician prescribes for patients with psoriasis, we found it...
important and necessary to examine this separately. A systematic review is presented here including published literature concerning rates of nonadherence, determinants influencing on nonadherence, and report if any designed interventions have been able to improve adherence in psoriasis treated with topically prescribed corticosteroids and corticosteroid combinations.

### Material and methods

#### Sources

We performed a systematic literature search for peer-reviewed articles in English in six major databases: Pubmed, Embase, Cochrane Library, Cinahl, Web of Science, and PsychINFO. The search included studies from inception in database until 22 September 2015.

#### Search strategy

Literature search followed a three-block search strategy using combinations of the following terms: psoriasis, adherence, and products containing topical corticosteroids, full search strategy available from [http://goo.gl/023tTY](http://goo.gl/023tTY). The literature search was performed according to a prespecified protocol registered at Prospero, reg. no. CRD 42015026283. The design was built according to the Assessing the Methological Quality of Systematic Reviews (AMSTAR) checklist (25), which has been reported to be reliable and valid (26).

#### Inclusion criteria

We considered cohort studies, population-based studies, randomized controlled trials, controlled clinical trials, surveys, interview studies, focus groups, and ethnographic studies.

#### Primary outcomes

Medical adherence either reported by patients or measured by an investigator.

#### Evaluation of eligibility of studies

Duplicate independent study selection was done independently by MTS and KEA. The sorting process was performed using Covidence® software. Inconsistencies were resolved by consensus.

### Quality assessment

The scientific quality of included articles was assessed by MTS and KEA. For included prospective studies, register-based studies, cross-sectional studies, and interventional study, a quality assessment table was designed for the specific requirements of this review, see Tables 3–5. The quality table was inspired by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist (27) of items that should be included in reports of observational studies. For qualitative studies, the quality checklist, see Table 5, was inspired by The National Institute for Health and Care Excellence (NICE) guideline (28). Quality was assessed as least adequate, adequate, and optimal. Studies were judged to have low risk of bias if they had optimal quality in at least five out of seven quality domains and no domains with least valuable quality. Studies with medium risk of bias were those with five or fewer optimum quality domains with only one least valuable quality domain. High risk of bias was defined as more than one least valuable domain (Tables 3–5). Quality assessment was done independently by MTS and KEA. Inconsistencies were resolved by consensus.

### Data extraction

MTS and KEA independently abstracted data from identified studies using a standardized data abstraction form, see Table 1. Determinants increasing nonadherence are presented in Table 2. Inconsistencies were resolved by consensus. Metanalysis was not planned, due to the limited number of studies and few study participants (40), heterogeneity of outcome measures, and heterogeneity in study design.

### Results

#### Study selection

The study selection process is illustrated in Figure 2; list of excluded studies is available from [http://goo.gl/023tTY](http://goo.gl/023tTY). A total of 11 studies were included. Ten studies addressed outcomes and determinants of nonadherence (29–34, 36) and one study reported an intervention designed to improve adherence (39).

#### Quality assessment

Quality assessments are presented in Table 3–5. The quantitative studies had an overall high risk of bias due to smaller samples, use
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Country</th>
<th>Setting</th>
<th>No. of patients</th>
<th>Age patients (years)</th>
<th>Type of topical corticosteroid</th>
<th>Measurement adherence</th>
<th>Nonadherence rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaghloul et al. (29)</td>
<td>Single blinded prospective 3-month study</td>
<td>UK</td>
<td>Hospital outward</td>
<td>201 (93 drop-outs)</td>
<td>18–65</td>
<td>Not specified</td>
<td>Patient reported on interval scale* in interview Medication weight</td>
<td>Patient-reported: 8% medication weight: 39.4%</td>
</tr>
<tr>
<td>Brown et al. (30)</td>
<td>Questionnaire</td>
<td>United States</td>
<td>Dermatology outward clinic</td>
<td>53 (28 nonresponders)</td>
<td>mean age 43</td>
<td>61% medium and 71% high-potency corticosteroid</td>
<td>Patient reported on nominal scale*</td>
<td>40%</td>
</tr>
<tr>
<td>Storm et al. (31)</td>
<td>Single-blinded prospective 14-day study</td>
<td>Denmark</td>
<td>Dermatology outward clinic</td>
<td>3</td>
<td>47–59</td>
<td>Not specified</td>
<td>Patient reported on nominal scale* Medicine weight: 100% Medication weight: 31–56% 1 patient primary nonadherent</td>
<td>Patient-reported: 52%</td>
</tr>
<tr>
<td>Ersser et al. (32)</td>
<td>Focus groups</td>
<td>UK</td>
<td>General practice</td>
<td>22</td>
<td>Mean age 61</td>
<td>Not specified</td>
<td>Patient reported</td>
<td>Participants used topicals ad hoc</td>
</tr>
<tr>
<td>Feldman et al. (33)</td>
<td>Questionnaire</td>
<td>United States</td>
<td>Online questionnaire</td>
<td>167</td>
<td>Mean age 49</td>
<td>Not specified</td>
<td>Patient-reported on nominal scale*</td>
<td>25%</td>
</tr>
<tr>
<td>Chan et al. (34)</td>
<td>Questionnaire</td>
<td>UK</td>
<td>Dermatology outward clinic</td>
<td>98 (26% non-responders)</td>
<td>Age &lt; 16</td>
<td>Not specified</td>
<td>Patient reported on interval scale*</td>
<td>46%</td>
</tr>
<tr>
<td>Bewley et al. (35)</td>
<td>Mixed-method: ethnographic and questionnaire</td>
<td>Canada, France, Germany, Italy, Spain, UK, United States</td>
<td>Online questionnaire</td>
<td>Ethnographic: mean age 42</td>
<td>Not specified</td>
<td>In questionnaire study: patient reported on nominal scale*</td>
<td>3 months: 66.6% 12 months: 83.3%</td>
<td></td>
</tr>
<tr>
<td>Svedbom et al. (36)</td>
<td>Register-based</td>
<td>Sweden</td>
<td>Register-based</td>
<td>16 154</td>
<td>Mean age 51.7</td>
<td>Mometasone and betamethasone/calcipotriol combinations</td>
<td>Non-persistence registered on interval scale*</td>
<td>75.5% low adherence</td>
</tr>
<tr>
<td>Saeki et al. (37)</td>
<td>Questionnaire</td>
<td>Japan</td>
<td>Online questionnaire</td>
<td>216</td>
<td>Mean age 46.3</td>
<td>Not specified</td>
<td>MMAS-8* translated into Japanese‡</td>
<td>59.7%–71.1%</td>
</tr>
<tr>
<td>Berroni et al. (38)</td>
<td>Questionnaire</td>
<td>Italy</td>
<td>Dermatology outward clinic</td>
<td>495</td>
<td>Mean age 52.6</td>
<td>Not specified</td>
<td>Patient reported on a four-point ordinal scale*</td>
<td>Week 1: 5.5 Week 9: 6.8</td>
</tr>
<tr>
<td>de Korte et al. (39)</td>
<td>Interventional</td>
<td>England, Ireland, Netherlands, Spain</td>
<td>Dermatology outward clinic</td>
<td>288 (42 drop-outs)</td>
<td>Mean age 43.5</td>
<td>Not specified</td>
<td>Patients reported on a seven-point ordinal scale*</td>
<td>Week 1: 5.5 Week 9: 6.8</td>
</tr>
</tbody>
</table>

*Non-validated scale; †MMAS-8, Morisky Medication Adherence Scale-8; ‡validated scale.
Table 2. Determinants increasing nonadherence.

<table>
<thead>
<tr>
<th>Determinant factors grouped after World Health Organization five dimensions of adherence (20)</th>
<th>Determinants studied in included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social/economic</td>
<td>Zaghloul et al. (29)* – single, male, unemployed, low quality of life, being too busy, paying for medication. Chan et al. (34)* – being too busy, cigarette smoking.</td>
</tr>
<tr>
<td>Healthcare-related</td>
<td>Ersser et al. (32) – low confidence towards their general practitioners, lack of education about how treatment work.</td>
</tr>
<tr>
<td>Disease-related</td>
<td>Zaghloul et al. (29)* – increased disease extent.</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>Zaghloul et al. (29)* – two applications per day.</td>
</tr>
<tr>
<td>Patient-related</td>
<td>Zaghloul et al. (29)* – being fed up, forgetfulness.</td>
</tr>
</tbody>
</table>

*Significance level with bivariate association, p < 0.001. †Significance level with bivariate association, p < 0.05.

Figure 2. Trial flow depicting the selection process of studies included in this study.

of nonvalidated patient-reported adherence rates, and lack of information regarding response rates. Publication bias was not addressed due to the limited amount of included studies (41).

**Rates of nonadherence**

Rates of nonadherence reported by patients on nonvalidated scales ranged from 8 to 88% in studies including from 53 to 16,154 patients conducted over various observation periods (29,30,33–38), see Table 1. Saeki et al. (37) used a validated scale for patient-reported rates of nonadherence, the Morisky Medication Adherence Scale-8 (MMAS-8) (42), and found that 75.8% of patients reported low adherence (37). In a subset of the small study by Storm et al. (31) including only three patients with psoriasis, three measurements of nonadherence rates were used: register-based for primary nonadherence, nonadherence reported by the patient on a nominal scale, and by medication weight. One patient was primary nonadherent. The remaining two psoriasis patients were completely nonadherent with regard to application of the prescribed number of doses the day before answering the questionnaire at end of a 14-day study period, but nonadherence was 31–56% by medication weight (ratio applied by weighed drug container/expected amount used at end of study period). In contrary, in the study by Zaghloul et al. (29), the patient-reported nonadherence rate was 8% (ratio applied by patients interviewed about applied amount of treatment at end of study period/expected amount used at end of the 3-month study period), but 39.4% by medication weight (ratio applied by weighed drug container/expected amount used at end of study period). The use of topical corticosteroids was also investigated in a Swedish register-based study (36). Nonpersistence was reported as patients who had not redeemed a second prescription. Nonpersistence on this nominal scale was 88.3% one year after the first prescription.

**Type of corticosteroid or corticosteroid combinations investigated**

Exact type of corticosteroid prescribed was only recorded in the Swedish study (36) where medical adherence to mometasone and combinations of betamethasone/calcipotriol was addressed. Remaining studies (29–35,37,38) mentioned topical corticosteroids but not the exact type of prescribed treatment.
Determinants increasing medical nonadherence

In a World Health organization (WHO) consensus report (20), it was proposed to categorize reasons for nonadherence into the following factors: social/economic, health system-related, disease-related, treatment-related, and patient-related. Thirty-four determinants of nonadherence are reported in Table 2. The determinants were reported by patients in surveys and interview (29,30,33–35,38) or focus groups (32). Three studies (29,30,34) reported a statistically significant correlation between the determinants increasing nonadherence, see studies listed below.

Social/economic factors

Factors increasing the risk of medical nonadherence included being single, male, unemployed, having a low quality of life, being busy, and paying for medication (29). Feldman et al. also reported paying for medication (33). In addition, a third study reported being too busy and cigarette smoking (34).

Health system-related factors

Low expectation of health service support, inadequate patient education, and lack of information about the optimal use of topical corticosteroids were reported as barriers to self-management, and were all determinants of nonadherence (32,35,38).

Disease-related factors

Patients with facial and more extensive disease were often nonadherent in one study (29), and patients with nonvisible areas affected were often nonadherent in another (38).

Treatment-related factors

The prescribed topical drugs were inconvenient in use, greasy, too oily, and difficult to apply (30,34,35,38). Frustration with medication efficacy and low medication efficacy were also reported (30,33,35,38). Further factors included the time used for application, two applications per day, the choice of vehicle, and being treated with a combination of several treatments (29,33,35,38).

Patient-related factors

Fear of side effects, forgetfulness, and being fed up with having psoriasis were reasons for nonadherence (29,30). Feldman et al. also reported using medication only when needed and avoiding prescription medication unless absolutely needed (33).

Designed interventions to improve medical adherence

de Korte et al. (39) reported an open multinational European interventional study conducted by dermatologists and dermatology nurses at dermatology clinics. The intervention consisted of three face-to-face consultations distributed over two months. The consultations included disease education, disease management training, and psychological support. Except use of the validated Skindex-29 and EuroQol-five dimensional questionnaire (EQ-5D), the study used study-specific nonvalidated patient reported outcome measures. The intervention significantly improved patient-reported rate of adherence, quality of life, and patient satisfaction at follow-up at week nine.
Discussion

Principal findings

In nine studies (29–31,33–35,37–39), nine different patient-reported measurements of nonadherence rates were used. Only one study used a validated patient-reported outcome of adherence (37). Two studies (29,31) used medication weight, and the other two studies (31,36) used prescription refill registers. In larger-scale studies, the diversity in self-reported nonadherence rates ranged from 8% to 88.3%. Since the authors have viewed at the complex issues using different measurements of nonadherence rates, it makes it difficult to draw a conclusion and compare studies. One multidimensional intervention could improve adherence (39). Thirty-four multifactorial determinants, among these 16 reported statistically significant, increased adherence. Only one study reported type of topical corticosteroid used.

Strengths and weaknesses of this study

This systematic review solely addresses nonadherence in psoriasis patients treated with topical corticosteroids or corticosteroid combinations. The extensive search strategy and broad inclusion of types of studies allowed us to get a comprehensive review of available literature, but at the same time our search strategy has limited precision. In addition, our literature search missed some drug utilization studies which also address medical nonadherence in terms of discontinuation of topical corticosteroids (43) and adherence to topical treatments (44). A qualitative study addressing nonadherence in relation to formulations of topical corticosteroids was not taken into account (45) and a study addressing rates of primary adherence was not included in the study Table 1 (15). From included studies, we could not clearly discriminate between intended and nonintended nonadherence. For simplicity, we focused on measurements of rates of medical adherence, with little attention to secondary outcome measures, e.g. patient reported outcome measures such as Quality Of Life (QOL) and Psoriasis Area Severity Index (PASI) scores.

Much is written about medical nonadherence to topical corticosteroids and corticosteroid combinations in patients diagnosed with psoriasis, although only few and heterogeneous original studies have been conducted. The recommendations from a systematic review without the potential for data synthesis cannot be more solid than the studies included.

Thorneloe et al. (23) addressed medical adherence to both systemic and topical treatment regimens in psoriasis patients and also found studies too heterogeneous to draw clear conclusions regarding determinants of nonadherence, in accordance with Devaux et al. (24) who studied nonadherence to all topical remedies used in treatment of psoriasis. Our study included five new studies (33–38) published since the works by Thorneloe and Devaux. The studies introduced use of the validated MMAS-8 (37), prescription refill records in a larger-scale study (36), and also ethnographic methods (35) in assessing determinants of nonadherence.

Possible mechanisms and implications for clinicians and policymakers

The diversity in self-reported nonadherence rates (29–31,33–38) may be explained by differences in questionnaires, differences in instructions to patients on how to report adherence, variation in sampling of psoriasis patients, and different study settings (36). The MMAS-8 was not only originally developed for hypertensive patients, but has also been validated for use in both oral and topical treatments in dermatology (42). Saeki et al. (37) used the MMAS-8 in a study of 237 psoriasis patients and found higher rates of adherence to systemic than topical treatments. Psoriasis is a chronic disease demanding intermittent topical treatment episodes, and the MMAS-8 seems less applicable in measuring rates of nonadherence in intermittent treatments.

Overall, the heterogeneity in measurement of adherence is in accordance to previous systematic reviews assessing medical adherence to topical products in psoriasis patients (23,24). For other chronic diseases, determinants of medical nonadherence are also reported to be multifactorial, see Kardas et al. (21).

Zschocke et al. (46) have designed the Topical Therapy Adherence Questionnaire (TTAQ) and Patient Preference Questionnaire (PRQ). These questionnaires are currently under evaluation for their usefulness in capturing patients’ priorities and screen for possible nonadherent patients, but they are too comprehensive to be used in daily practice.

The long-term effect from the intervention by de Korte et al. (39) is unknown, since no follow-up visits after study termination were reported. The open design can be a confounder and all types of interventions can influence on rates of adherence (47). Further, patients self-reporting their rates of adherence tend to be overoptimistic (48).

In psoriasis patients, a study demonstrated that adherence to topical treatment with salicylic acid dropped during treatment course (49) and in another study adherence to salicylic acid increased around office visits (50). van de Kerkhof et al. (51) reported that the combination of calcipotriol cream morning and ointment evening can improve adherence compared to twice-daily ointment. These associations may be the same for psoriasis treated with topical corticosteroids or corticosteroid combinations.

A questionnaire study by Halioua et al. (52) addressed determinants of refusal to prescribed topical corticosteroids. Even though this is a field that needs to be described in further research, active refusal to receive a prescription cannot be categorized as primary nonadherence.

Conclusion

Recommendations for future research

Studies addressing determinants of nonadherence

This review justifies future research addressing determinants of nonadherence and intervention to improve adherence in psoriasis treated with topical corticosteroids and corticosteroid combinations. Future studies need to address the many determinants for medical nonadherence using careful-designed protocols focusing on one or few factors at a time, because if too many determinants are included simultaneously it may be unrealistic to achieve firm conclusions. The wishes and expectations of the individual patient must be taken into account and rates of nonadherence should be measured in relation to: extent and severity of psoriasis, duration of treatment, amount of applied topical corticosteroids, numbers of treatments per day, information about how physician inform the individual patient when their prescription is issued, length of office visits, interval between office visits, and combinations of creams and ointments. To better reveal actual rates of nonadherence (47), drug utilization studies should be conducted based on prescription-refill registers (53).

Studies testing interventions to improve adherence

To help in the implementation process, medical professionals could learn from experiences from psoriasis patients (32).
Therefore, we recommend additional qualitative studies focusing on patient's perspectives and beliefs concerning treatment with topical corticosteroids. Patients’ experiences can be implemented, ensuring the patients have both power and knowledge to follow a treatment plan based on patient-centered shared decision-making (54).

From other chronic diseases only interventions using multiple interventions have proven successful (19). In a study (21) 771 individual determinants of nonadherence were identified, most of them influencing on implementation. Only 93 of the determinants were identified in behavioral interventions. The conclusions from this review are in agreement with recommendations from the Cochrane group (19): randomized controlled trials should be conducted with sufficient power to test interventions to improve adherence; the purpose of the study should be blinded for the patients in an adherence intervention; the intervention could encompass the use of technical support (55) (e.g. apps for smartphones); the topical formulation and exact type of corticosteroid or corticosteroid combination should also be considered (45).

Researchers are recommended to use the same outcome measures of the highest quality and reliability for the actual setting (56,57). Studies need to measure rates of medical adherence assessed as calculated topical products to be used according to surface area to be treated divided by actual weight of medication used at end of the study period. Further, primary nonadherence should be assessed by searching prescription refill registers. In addition to measurement of adherence rates, it is a necessity to obtain secondary outcomes measures [e.g. the validated Self-Administered Psoriasis Area Severity Index (SAPASI) (58) and Dermatology Life Quality Index (DLQI) (59)]. Long-term effects need to be measured six months after termination of the adherence-improving intervention. To our knowledge, to date no studies in dermatology have met these criteria.

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Disclosure statement

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References


