Quantitative analysis of topical treatments in atopic dermatitis

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Topical treatments in atopic dermatitis: unexpectedly low use of emollients; use of topical corticosteroid is higher in juvenile patients, higher in male vs females, and shows independent associations with asthma and depression

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running head: quantitative analysis of topical corticosteroid and emollient treatment in eczema

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What's already known about this topic?

- Both emollient and topical corticosteroid treatment (TCS) have been a mainstay of eczema treatment for >60 years but the actual quantities used by patients under real-world conditions are unknown.

What does this study add?

- Real-world use of emollients is four-fold lower than current guidelines. Underuse of emollients may be a significant factor in disease exacerbation.
- Use of TCS is significantly higher in male patients.
- Use of TCS is higher in patients who also have asthma.
- Use of TCS is strongly associated with concurrent anti-depressive treatment.

Abstract

BACKGROUND: Despite decades of use,the actual amounts of topical corticosteroids (TCS) and emollients used in moderate-to-severe atopic dermatitis (AD) under real-world conditions are unknown. Thus, it remains unclear if inadequate use is widespread. OBJECTIVE: To quantify the use of TCS and emollients in moderate-to-severe AD. METHODS: Double-blinded drug prescribing recorded prospectively at the point of drug dispensing within a catchment of approx. 450,000 over a 31-year period in a population-

based cohort marked by failure of disease control in primary care (n = 844). For each patient, prescribing was recorded over 12-month to minimize fluctuations. RESULTS: The resulting dataset was near-complete, and essentially free of reporting- and recording bias. Atopic co-morbidities matched expected frequencies. Median use of TCS was statistically significantly higher in juvenile (age < 16) compared to adult patients (49.2 vs. 38.1 gram / month), in males vs. females (46.8 vs. 29.7), and in patients receiving concurrent asthma treatment (40.4 vs. 26.7). TCS use was strongly associated with anti-depressant treatment. Emollient use was unexpectedly low at median of 9.6 gram/day (range 1.4 – 30.1). Results replicated in an independent validation cohort. CONCLUSIONS: Deficient use of emollients may be a factor contributing to AD severity. TCS use does not exceed current guidelines. Accurate quantification of topical treatments provides a widely accessible strategy to measure real-world impact of novel AD treatments.

Introduction

Topical treatment with emollients and corticosteroids, the latter first manufactured in the 1950s, has been for decades a cornerstone of treatment for atopic dermatitis (AD), previously designated 'neurodermatitis'. Precise quantitative data on the actual amount of these agents used have been compiled in a few interventional clinical trials (e.g. [1], reviewed in [2]) but are lacking from routine clinical practice beyond estimates in small samples [3], posing a notable knowledge gap [4]. As a consequence, it is uncertain how many patients (juvenile and / or adult) undergo disease flares or shifts in severity patterns due to inadequate topical treatment. Furthermore, it is unclear whether topical treatment significantly differs among different age ranges and between genders. The ability to measure "consumption" of

topical treatment would also provide a useful outcome measure to assess the impact of emerging new drug-based AD treatments, e.g. IL4/IL13 , IL13, or JAK1 [5-7].

We here employed electronic data capture to address this knowledge gap. In a population catchment of 450,000, essentially all medical treatment is dispensed by a single provider (NHS Tayside), with private providers accounting for less than 5 percent of treatment [8, 9]. All drug prescribing is prospectively electronically captured, as are specialist-led diagnostic verification and concurrent other dermatological diagnoses. These resources allow both quantitative analysis of topical treatments, as well as proxy-assignment of medical diagnoses based on drug prescribing.

Using this data resource, we here report a detailed quantitative analysis of both topical corticosteroid and emollient used in moderate-to-severe AD. Our data reveal a number of unexpected associations between drug usage, comorbidities, and other factors. Importantly, our data suggest that "the quantitative measurement of topical treatments in AD through retrieval of health data records is accessible for many health care providers and could provide a readily available measure of efficacy for newly introduced drug treatments."

Materials and Methods

Ethics statement: All data generated in this study were obtained in accordance with the Declaration of Helsinki and in compliance with local governance approval regulations (Approval by: NHS Tayside Caldicott guardian committee, approval number IGTCAL4187++; Photonet, IGTCAL3519; R&D, 2017DS08). In accordance with local governance regulation, patient identifiable information was anonymized by the Health Informatics Centre Tayside (HIC; www.farrinstitute.org).

STROBE statement: This is an observational cohort study. In accordance with the STROBE checklist [10], background and objectives are specified in the Introduction. Design, setting, participants, variables, data sources, quantitative variables, statistical methods used, and bias (reporting as well as selection) are discussed below and in Results. All other elements listed in the STROBE checklist, specifically Limitations, are listed in Results and Discussion.

Study design: This study employs combined prospective / retrospective design elements as follows: Study endpoints, including all parameters of drug usage, IgE results were collected prospectively and double-blinded (see below). Study design, analysis, and data interpretation were performed retrospectively. Details on observational window and patient cohort assembly are given below.

Observational window: The observational window for this study was defined between 1 January 1986 to 1 September 2017. This observational window was chosen as maximal period yielding complete coverage of prescribing information, laboratory data, and demography-linked data.

Patient selection strategy: The aim of the study was to quantify drug usage in patients with AD of moderate-to-severe extent with disease affecting not only selected body sites. Mild-to-moderate AD is managed within primary care in Scotland. Once referred to secondary care, the triage/treatment pathway operative in NHS Tayside is as follows: if the condition is manageable with topical treatments, issue advice and discharge back to GP. If not, consider phototherapy (specifically NB-UVB). If not suitable (for any reason), consider addition of systemic drugs to topical treatments. Therefore, in order to identify AD patients not controlled by topical treatments, patients were initially screened using the Photosys database (www.photonet.scot.nhs.uk). This screen was simultaneously used to exclude

patients clinically assessed to require treatment only to localised sites (e.g. scalp, hands only). The resultant initial dataset of n = 859 patients were largely naïve to third line treatments (see Results, Table 1).

Cohort refinement and validation: The Photosys-derived dataset was linked with a dermatology-curated database (Dermabase). This linkage allowed for verification of AD diagnosis as well as identification and elimination of concurrent dermatological diagnoses as confounders. Fifteen patients had other diagnoses at the time of referral (e.g. psoriasis, urticaria, acne), leaving a total of n = 844. 5.6 % of patients within this final cohort had recorded other concomitant skin conditions. Data were analysed with and without this subset to exclude confounding effects (Table S1).

Prescribing information, clinical profiling and data refinement: The cohort delineated above was linked to the Scotland-wide drug prescribing database. This identified 424,584 prescription incidents. These were linked with prescription items and matched with the clinical patient cohort (n= 844), yielding a total of 351,673 prescriptions. Prescriptions filled outside of the observational window (12 months before initiation of phototherapy) were removed, leaving a final of n= 29,929 verified prescription incidents.

Quantification of drug prescribing: All drug quantities analysed were recorded at the time of dispensing. AD-relevant medications prescribed to the clinical patient cohort were recorded by section code in the British National Formulary (BNF). This, a list of emollient and TCS items, along with an analysis of compliance and quantity distribution analysis, is detailed in the Supplement.

Quantification of IgE: The IgE status of the patient cohort was obtained from HIC. IgE levels were measured in kU/l with local reference values for normal range in adults being 5 -120 kU/l. IgE data were available for n = 301 patients. IgE entries had accumulated for this

sub-cohort independently of referral to dermatology and consequently had been recorded unrelated to the observational window used for drug prescribing. Therefore, for the purpose of the present study, IgE values were employed as a proxy for "maximal observed IgE potential" for a given individual and not in relation to AD severity. Consequently, whenever multiple IgE entries were available for an individual patient, the highest IgE value (rather than average) was recorded.

Assembly of control population cohort: Data on the control population cohort (Table 1) was retrieved from National Records of Scotland (NRS) and the Information Service Division (ISD) Scotland as detailed in the Supplement.

Calculation of body surface area (BSA) versus frequency of TCS application (see Figure 1c) in relation to current guidelines: The principle quantity known from the primary data extracted from health records was the monthly amount of TCS dispensed per patient. Since the median amount of TCS applied is about 20% higher in male patients ([11]), we adjusted the gender – specific amount of TCS required for a single 100% BSA coverage accordingly (20 g in males vs. 16 in females) in line with commonly used amounts [12]. We then calculated the frequencies of applications which each patient's observed TCS use would correspond to, assuming a range of affected BSA percentages, using the formula:

$$Nr\ of\ monthly\ TCS\ applications = \frac{Observed\ TCS\ use}{TCS\ use\ for\ 100\%BSA} \div involved\ BSA\ (\%)$$

In order to account for the observed large inter-individual differences we performed this not only with the median observed TCS amount but also with the 25th and 75th percentiles, respectively, of the TCS quantities used in this cohort to encompass the overall range of observed TCS amounts. The resultant graph (Fig.1c) shows the number of

applications per month consistent with our data over a wide range of potentially BSA-percentage that TCS was applied to.

Current guidelines [NICE TA81] (https://www.nice.org.uk/guidance/ta81/chapter/1-Guidance) state that "topical corticosteroids for atopic eczema should be prescribed for application only once or twice daily." Current SIGN guidelines state "Patients with atopic eczema should be advised to apply topical corticosteroids once daily." (https://www.sign.ac.uk/assets/sign125.pdf)

Statistical Methods. Data analysis and statistical tests were carried out using Stata 14.0 package (Stata Corp 2015, College Station, TX). Specific tests applied for detection of significance are indicated in each respective table and figure legend.

Results

Clinical profile of AD patients not controlled in primary care. The most important factor impacting on AD treatment is actual disease severity. This is not routinely recorded by quantitative scales in clinical practice. In order to capture "more-than-mild" AD severity we therefore here used a selection strategy using the criteria: (i) patients seen repeatedly by their GP's and referred to secondary care, (ii) triaged by consultant-led dermatology review as unfit for discharge, (iii) assessed as requiring full body (as opposed to "localised site" only) phototherapy. While AD naturally fluctuates in severity, patients in this cohort therefore exhibited severity requiring specialist assistance at least on three occasions during the 12-months observational window: first, at GP-review leading to referral; second, at dermatology review (which they did not fail to attend); third, at initiation of phototherapy. It is thus a conservative assumption that a "moderate" severity was present for at least 12 weeks out of 52 weeks (four week interval before each clinical contact) which is characterised by 16 - 30

% body surface area involvement.[13] The age distribution in the resulting cohort (Fig. S1a) reflects the cumulative referral-activity among all local GPs and exhibits a bi-modal distribution with a large peak in the 16 - 25 year range and a broader peak among older patients in addition to juvenile patients. We therefore mapped all subsequent age-related subgroup analyses (see below) to three age-range subsets represented in this cohort (0 – 15 / 16 – 25 / 26+), respectively. In terms of social socioeconomic status, the patient cohort did not show bias toward either wealthier or deprived areas (Fig. S1b). As expected, this cohort exhibits a high prevalence of atopic co-morbidities, as well as anti-histamine use (Table 1). Additional data on drug treatment unrelated to atopic disease do not indicate association of AD with a range of other medical conditions (Table S2).

Unexpectedly low use of emollients. Table 2, Figure 1a and Figure 1d (left) show median, box plot, and distribution, respectively, of average daily emollient usage during the year preceding referral to secondary care. Emollient usage ranged between 4.6 – 16.8 g / day (25^{th} and 75^{th} percentiles; median: 9.6) for adults and 12 – 30 g / day (median: 17.5) for juvenile patients, respectively (Fig. 1a) and did not differ significantly between genders. Although the observed use varies between patients, the median overall daily use of approx. 10g (less than 5g in the lowest quarter, see Fig. 1a) implies that many patients hardly use any emollients at all for large time periods throughout one year. This is in stark contrast to current guidelines recommending dispensing of 85 g /day (600g / week) for adults and 35 g / day (250g / week) for children, respectively. [14]

Confirmation of emollient use in an independent replication cohort. Since the data summarised above appeared much lower than expected, we initially performed an exhaustive data quality analysis which failed to identify any discernable source for data loss during IT-processing (see Supplement). However, the overall capture rate of drug prescribing by ISD Scotland is not 100 %. Specifically, in our cohort we noted an only 88 % prevalence of

emollient use and 90 % prevalence of TCS use (Table 1). We therefore assembled an entirely independent replication cohort, consisting of all patients referred to secondary care after the original cut-off date (1 Sept 2017, n = 138). Indeed, prevalence of both emollients and TCS in this cohort exceeded 97 %, confirming a near-complete rate of data capture by ISD Scotland (File: Replication Cohort). Accordingly, there was a slight increase of overall daily emollient use (median 12.8 vs. 9.6), as well as TCS use (see below). This entirely independent dataset, however, did not yield substantially different outcomes. We conclude that, at least in north-east Scotland, real-world use of emollients is almost four-fold lower than current guidelines.

Median use of TCS in moderate-to-severe AD does not exceed guidelines. The box plot and median use of TCS are shown in Fig. 1b and Table 2, respectively. Distribution of use is shown in Fig.1d (right). A correlation analysis between emollient and TCS use is shown in Fig. S2). Monthly amounts range between 25 – 70 g (25^{th} and 75^{th} percentiles, respectively; median: 47) in males and 16 – 53 (median: 30) in females. In terms of potency class, as expected, children received lower potent TCS more commonly than adults (Table S4). These data did not change appreciably after exclusion of patients with concurrent other dermatological diagnoses (psoriasis, urticaria, discoid eczema), confirming that AD was the principle driver for the observed TCS use (see Table S1). Furthermore, knowledge of TCS quantities allows an estimation of the frequency of application (see Methods). Thus, assuming a median of 20 g required for a male and 16 g for a female full body application, respectively, and accounting for known inter-individual variabilities [11, 12], the TCS use observed in this cohort is consistent with anywhere between 5 – 60 TCS applications per month across a wide range of possible body surface area sizes (Fig. 1c). This level of use does not exceed current guidelines (see Methods). Clearly, inter-individual differences are large. However, across the cohort excessive TCS use does not appear to be highly prevalent.

Higher TCS use in male patients. Unexpectedly, as detailed above, we observed a highly statistically significant gender imbalance among adult patients. The higher TCS use in male patients exceeds what could be attributable to the 20 % difference in body surface area (BSA) divergence (see Methods) [11]. There is no apparent explanation accounting for this observation.

High prevalence of antibiotic and oral systemic treatment. We next analysed general drug use by AD patients compared to population controls. As shown in Table S2, AD patients exhibited age-adjusted treatment profiles identical to background population treatments for a wide range of conditions. The two notable exceptions were the prevalence of antibiotic use (28.8 % vs. 5.7 %) and oral systemic corticosteroid use (4.4 % vs. 0.7%). This was partly owed to the concurrent high prevalence of asthma (Table S3), although even in the asthma-negative patient subgroup both oral systemic corticosteroid and antibiotic treatment was more common than in the control population (Table S3, antibiotic prevalence: 20.0%, oral systemic steroids: 2.3 %).

Increased use of topical corticosteroids in patients requiring asthma treatment. Although asthma is associated with AD, reliable data on the effect of asthma on the severity of AD are lacking [15]. The availability of accurate quantitative treatment data allowed us to explore the effect of asthma. As expected, use of systemic oral corticosteroids, antihistamines, antibiotics, as well as antidepressants [16] was higher in AD patients requiring treatment for asthma (Table S3). Unexpectedly, however, we also observed a small but statistically significant increase in the number of patients using topical corticosteroids in this subgroup in all age ranges but especially in older adults (Table 3). The amount of topical corticosteroids used per patient was also increased, especially in the juvenile and in the >25 age groups, respectively (Fig. 2a). This was observed in both genders but was even more pronounced in female patients (Fig. S3). In fact, we observed a clear linear correlation

between the amount of asthma-inhalers used and the use of corticosteroid (Fig. 2b). The apparent effect of Asthma-inhaler usage on topical corticosteroid treatment was independent of IgE level, but concurrent IgE elevation and active asthma had an even greater effect (Fig. S4). We conclude that, at least in this population, concurrent therapy-requiring asthma impacts on the quantity of topical corticosteroids applied by AD patients.

Topical corticosteroid use is associated with high prevalence of antidepressant treatment, independently of asthma status. Sub-group analysis based on asthma status had shown an association between antidepressant treatment and asthma (Table S3) as well as between asthma and the use of topical corticosteroids (see above). We therefore asked if the former association was in fact explained by the use of topical corticosteroids. For this purpose, we grouped the use of topical corticosteroids in low vs high, choosing a cut-off 50 g / month based on the distribution of topical corticosteroid use in our population (Fig. 1d right). We limited analysis to adult patients since anti-depressant use was virtually absent in juveniles (Fig. S5). As shown in Table 4, the prevalence of regular anti-depressant treatment was almost doubled in patients applying high amounts of topical corticosteroids (12% vs. 6%) and this difference was retained in non-asthma patients.

Discussion

Topical corticosteroids and emollients have been the mainstay of AD treatment. Despite extensive study of mechanisms and efficacy in interventional trials, virtually no data exist on the actual amount of these compounds applied by patients under real-world conditions. The present report is a first step towards addressing this gap. Using a population-based database-mining approach, we here establish that, at least in Scotland, use of emollients dramatically differs from guideline recommendations. Half of AD patients use less

than 10 g per day, even after multiple GP consultations and referral to secondary care. Given that we extracted twelve-month-average use, the data imply that many patients evidently do not use emollients on a daily basis but only as/when they experience flares. Clearly, emollient use as a prophylactic to prevent exacerbation is not widespread, in direct contradiction to current guideline recommendations. Although the data presented here may differ from other populations, the data were replicated almost identically in an entirely independent cohort, ruling out deficient data capture. Likewise, it is unlikely to assume that a substantial fraction of patients would choose to buy over-the-counter emollients instead of utilising freely available compounds.

The TCS use observed here, between 20-65 gram / month, corresponds to roughly 0.75 – 2 applications per day across the whole year, which does not exceed guidelines. As shown in Figure 1c, an average once-daily application of the median observed TCS amount would equate to approximately 7.5% body surface area. Given that moderate AD equates to BSA involvement between 15-40%, it is therefore likely that patients, at least at the time of referral, dermatology review, and initiation of phototherapy, respectively, would exhibit higher BSA involvement. Even accounting for intervening periods of remission (which our data cannot capture), the observed level of TCS use would appear overall on the low end of the expected. In terms of underlying factors, the observed significantly higher use of TCS in juvenile patients (where parents may often be involved in treatment) suggests that "steroid phobia" ([17, 18]) is unlikely to be a major factor underlying moderate TCS use.

One of the difficulties in obtaining high quality real-world data is the definition of cohorts with relatively homogenous severity ranges. In this regard, we here employed an approach targeting a defined observational window prior to specialist-care referral, as well as specialist-based triage toward a full-body treatment approach. Our data clearly suggest that a moderate-to-severe cohort profile can be extracted from population based data in the absence

of dedicated scores, which are not routinely available. Prescribing data analogous to those held by NHS Scotland are available for many other health care providers, suggesting that the methodology presented here can be adapted widely.

We unexpectedly observed that patients requiring ongoing asthma-treatment use significantly higher amounts of *topical* corticosteroids (Fig.3). Although much has been written about concurrent atopy, including asthma, and the so-called 'atopic march', we were unable to identify any published reports on an effect of atopic co-morbidities on *skin*-targeted steroid treatment. The magnitude of the effect as well as independence of confounding additional atopic manifestations strongly argues against an artefact. Possibly, patients who are used to taking treatments for asthma could be more adherent to their topical treatments. Alternatively, or in addition, TCS, although prescribed and consciously applied to affect AD, might also contribute to asthma control via percutaneous absorption. A third possibility is that patients with coexisting asthma and AD have more severe disease.

We find that the prevalence of patients requiring repeat antidepressant prescriptions is twice as high in AD patients using high vs. low amounts of topical corticosteroids (12% vs. 6%, table 4). These data confirm previously reported associations between AD and depression in adults [19] and children [20] and further validate the use of quantitative drug prescribing data to obtain clinically relevant 'holistic' treatment read-outs. In this regard, perhaps the most obvious application of the approach presented herein will be the confirmation and quantification of benefit for AD patients of novel, and often resource-intensive treatments, e.g. dupilumab. Use of database-based real-world studies circumvents the need for dedicated feedback-elicitation, thereby reducing bias.

Finally, our data exhibit a number of obvious limitations. First, use of drug treatment as proxy for medical diagnoses may not capture clinically confirmed diagnoses in non-atopic conditions. Second, our data were obtained in a genetically rather homogenous population [21] and may be of limited predictive value for other populations. Third, there is a degree of uncertainty on the actual use of topical drugs, as quantities analysed here are recorded at drug dispensing (for details, see Methods). Forth, sub-analyses reported age-group specific findings by necessity exhibit limited numbers of observations.

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References

1. Fukaya M, Sato K, Yamada T, et al. A prospective study of atopic dermatitis managed without topical corticosteroids for a 6-month period. Clinical, cosmetic and investigational dermatology. 2016;9:151-8. PubMed PMID: 27445501. Pubmed Central PMCID: 4938118.

2. Siegfried EC, Jaworski JC, Kaiser JD, Hebert AA. Systematic review of published trials: long-term safety of topical corticosteroids and topical calcineurin inhibitors in pediatric patients with atopic dermatitis. BMC pediatrics. 2016 Jun 7;16:75. PubMed PMID: 27267134. Pubmed Central PMCID: 4895880.

3. Hon KL, Ching GK, Leung TF, et al. Estimating emollient usage in patients with eczema. Clinical and experimental dermatology. 2010 Jan;35(1):22-6. PubMed PMID: 19489850.

4. Drucker AM, Wang AR, Li WQ, et al. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. The Journal of investigative dermatology. 2017 Jan;137(1):26-30. PubMed PMID: 27616422.

5. Wollenberg A, Howell MD, Guttman-Yassky E, et al. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. The Journal of allergy and clinical immunology. 2019 Jan;143(1):135-41. PubMed PMID: 29906525.

6. Wang FP, Tang XJ, Wei CQ, et al. Dupilumab treatment in moderate-to-severe atopic dermatitis: A systematic review and meta-analysis. Journal of dermatological science. 2018 May;90(2):190-8. PubMed PMID: 29472119.

7. Venerology EAfDa. Upadacitinib Longer-Term (32-Week) and Patient-Reported Outcomes Data from Phase 2b Atopic Dermatitis Study 2018. Available from: https://news.abbvie.com/news/abbvie-presents-upadacitinib-longer-term-32-week-and-patient-reported-outcomes-data-from-phase-2b-atopic-dermatitis-study-at-27th-european-academy-dermatology-and-venereology-eadv-congress.htm.

8. West J, Ogston S, Berg J, et al. HLA-Cw6-positive patients with psoriasis show improved response to methotrexate treatment. Clinical and experimental dermatology. 2017 Aug;42(6):651-5. PubMed PMID: 28512993.

9. West J, Ogston S, Palmer C, et al. Methotrexate in psoriasis under real-world conditions: long-term efficacy and tolerability. The British journal of dermatology. 2016 Jun;174(6):1407-10. PubMed PMID: 26852010.

10. Editors TPM. Observational Studies: Getting Clear about Transparency. PLoS Med. 2014;11(8):e1001711.

11. Schlagel CA, Sanborn EC. The Weights of Topical Preparations Required for Total and Partial Body Inunction. The Journal of investigative dermatology. 1964 Mar;42:253-6. PubMed PMID: 14130641.

12. Oakley A. Fingertip unit 2001. Available from: https://http://www.dermnetnz.org/topics/fingertip-unit/.

13. Chopra R, Vakharia PP, Sacotte R, et al. Severity strata for Eczema Area and Severity Index (EASI), modified EASI, Scoring Atopic Dermatitis (SCORAD), objective SCORAD, Atopic Dermatitis Severity Index and body surface area in adolescents and adults with atopic dermatitis. The British journal of dermatology. 2017 Nov;177(5):1316-21. PubMed PMID: 28485036.

14. PCDS-BAD. Guidelines for the management of atopic eczema: National Centre for Clinical Excellence UK; 2009. Available from: https://http://www.nice.org.uk/guidance/ta81/resources/primary-care-dermatology-society2.

15. Celakovska J, Bukac J. The severity of atopic dermatitis evaluated with the SCORAD index and the occurrence of bronchial asthma and rhinitis, and the duration of atopic dermatitis. Allergy & rhinology. 2016 Jan;7(1):8-13. PubMed PMID: 27103554. Pubmed Central PMCID: 4837137.

16. Choi HG, Kim JH, Park JY, et al. Association Between Asthma and Depression: A National Cohort Study. The journal of allergy and clinical immunology In practice. 2018 Nov 10. PubMed PMID: 30423450.

17. Bos B, Antonescu I, Osinga H, et al. Corticosteroid phobia (corticophobia) in parents of young children with atopic dermatitis and their health care providers. Pediatric dermatology. 2019 Jan;36(1):100-4. PubMed PMID: 30338542.

18. Saito-Abe M, Futamura M, Yamamoto-Hanada K, et al. Topical corticosteroid phobia among caretakers of children with atopic dermatitis: A cross-sectional study using TOPICOP in Japan. Pediatric dermatology. 2019 Mar 18. PubMed PMID: 30882946.

19. Chiesa Fuxench ZC, Block JK, Boguniewicz M, et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. The Journal of investigative dermatology. 2018 Oct 30. PubMed PMID: 30389491.

20. van der Lee M, Arabkhazaeli A, van Erp FC, et al. Atopic dermatitis characteristics and medication-use patterns in school-age children with AD and asthma symptoms. Clinical and experimental dermatology. 2017 Jul;42(5):503-8. PubMed PMID: 28585727.

21. Nititham J, Fergusson C, Palmer C, et al. Candidate long-range regulatory sites acting on the IL17 pathway genes TRAF3IP2 and IL17RA are associated with psoriasis. Experimental dermatology. 2018 Nov;27(11):1294-7. PubMed PMID: 30076642.

Table 1. Clinical characteristics of the Tayside atopic dermatitis cohort[1]

	AD patients (n = 844)
Age (median ± s.d.)	25 ± 16.5
Juvenile (age ≤ 15)	8.2 %
Gender (% female)	53.1 %
Asthma[2]	243 (28.8%)
Elevated total IgE (%)[3]	249 (82.5%)
Allergic rhinitis (%)	93 (11.0%)
Anti-histamine use (%)	582 (69.0%)
Emollient use (F / M) (%)	745 (88.3%)
Topical corticosteroid use (F / M) (%)	762 (90.3%)
Oral systemic corticosteroid treatment	167 (19.8 %)
Other systemic treatment for AD[4]	6 (0.7 %)

[1] Clinical characteristics for patients not adequately controlled in primary care with minimum duration of 12 months AD (see Methods).

[2] Defined by regular use of BNF-coded preparations (see Methods).

[3] Defined as total IgE > 120 kU / l.

[4] Comprises methotrexate, cyclosporine, azathioprine.

Table 2. The amount of emollients and topical corticosteroids used by AD patients during a twelve month period before referral to secondary care.[1]

	Usage by age - range		
	0 – 15	16 – 25	> 25
TCS (g/month)	49.2 ± 50.4	35.0 ± 38.4**[2]	38.1 ± 49.8*[2]
Emollients (g/day)	17.5 ± 30.8	9.9 ± 13.3***[2]	9.6 ± 18.3***[2]
Emoll / TCS[3]	7.5 ± 1.4	6.5 ± 3.0	6.2 ± 3.6
	Usage by gender and age - range		
	TCS (gram / month)		
	0 – 15	16 – 25	> 25
Female	48.9 ± 54.5	32.5 ± 32.3*[3]	26.6 ± 32.7***[4]
Male	49.2 ± 47.1	37.5 ± 44.4	52.1 ± 58.2
	Emollients (gram / day)		
Female	15.2 ± 18.9	9.6 ± 11.7	7.9 ± 19.0*[4]
Male	18.4 ± 38.3	10.3 ± 14.9	10.1 ± 17.6
Emoll/TCS female[3]	7.5 ± 1.4	6.5 ± 2.4	6.5 ± 4.1
Emoll/TCS male[3]	7.5 ± 1.5	6.5 ± 3.7	5.7 ± 3.1

[1] Data shown represent median ± s.d., respectively, for all patient that have been treated with TCS (n = 762) and emollient (n = 745), respectively, as indicated in the table since data were non-Gaussian distributed (see Fig 1d). TCS subgroup sample sizes were for females: 0-15: n = 28, 16-25: n = 180, >25: n = 189; for males: 0-15: n = 31, 16-25: n = 148, >25: n = 186. Emollient subgroup sample sizes were for females: 0-15: n= 27, 16-25: n = 179, >25: n= 183; for males: 0-15: n = 31, 16-25: n = 144, >25: n = 181.

[2] between age-range significance (vs. age-range “0 – 15”): * $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$ (Kruskal Wallis rank test).

[3] ratios calculated for each patient, then by age groups.

[4] between-gender significance: * $p < 0.05$; ** $p < 0.01$, *** $p < 0.001$ (Wilcoxon rank-sum test).

Table 3. The association of topical corticosteroid use in AD patients with asthma status.[1]

Age-range (y)	**Prevalence of topical corticosteroid treatment**			
	Regular asthma – treatment[2]			
	no		yes	
	n	% [95 % C.I.]	n	% [95 % C.I.]
0 - 15	36	78 [66 – 91]	23	100 [--] *
16 - 25	243	89 [85 – 93]	85	96 [92 – 100] *
> 25	246	87 [83 – 90]	129	97 [95 – 100]**

[1] Percentage of AD patients receiving prescriptions for topical corticosteroids within 12 months before referral to secondary care.

[2] Defined as minimum of three prescribed asthma inhalers per twelve months (see Methods).

* $p < 0.05$, ** $p < 0.001$ (Pearson's chi-squared test).

Table 4. The association between use of topical corticosteroids and anti-depressant treatment.[1]

	Prevalence of patients using regular antidepressants			
	Topical corticosteroid usage:			
	Low[2]		High[2]	
	% [95% C.I.]	n	% [95% C.I.]	n
All patients	**7.6** [5.4 – 9.9]	524	**12.5** [8.2 – 16.8]*	232
Asthma: no	**6.0** [3.6 – 8.3]	400	**12.6** [7.0 – 18.1]*	143
Asthma: yes	12.9 [5.4 – 19.3]	124	12.4 [6.9 – 18.8]	89

[1] At least three repeat anti-depressant prescriptions in twelve months. Figures set in bold print met statistical significance. * p = 0.01 (Pearson's chi-squared test)

[2] Low: ≤ 50 g / month; High: ≥ 50 g / month (see Fig. 1d right for selection of cut-off).

Legends to Figures

Figure 1. The use of topical agents in moderate-severe AD. (a) Daily usage of emollients by gender (left), and broken down by age/gender (right). Boxplots show the median (horizontal bar), 25th and 75th percentile (boxes), as well as range (min/max), respectively, of average monthly usage across one year. (b) Same as in (a) for monthly use of topical corticosteroids. Horizontal lines indicate 50th percentile (** $p < 0.001$). (c) Projected number of applications per month of topical corticosteroid use for male (left) and female (right) patients based on the observed median (dashed line), as well 25th and 75th percentile use (grey shaded), across the range of possible body-surface-areas involvement. The boxed regions demarcate BSA percentages exposed to TCS at once to twice daily applications. The data show that less than median 5% BSA involvement across the cohort would correlate with more than twice-daily TCS application and is therefore highly unlikely. (d) Distribution of daily emollient use, shown in log format (gram / day, left, one bar represents 2g), as well as TCS, shown in linear format (gram / month, right, one bar represents 10g) broken down by gender. The horizontal lines on top in the TCS graph denote grouping into “low” vs. “high” groups of corticosteroid usage.

Figure 2. The association of topical corticosteroid use in AD with asthma. (a) Monthly corticosteroid usage broken down by age group and asthma requiring active treatment ("yes" = three or more inhaler prescriptions per year). * $p < 0.05$, ** $p < 0.01$ (t-test). (b) Correlation between the number of Asthma-prescriptions and monthly use of topical corticosteroid use. Asthma-treatment groups selected to generate even groups sizes between asthma-subgroups and were as follows: "0" = no inhalers (n = 520, "1" = 1 – 2 inhalers (average 1.7, n = 102), "2" = 3-7 inhalers (average: 5.6, n = 105), "3" ≥ 9 inhalers (average 16.6, n = 117).