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Use of topical antipsoriatic drugs in Denmark: a nationwide drug utilization study

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Summary

Background The reported real-life use of prescribed topical antipsoriatic drugs is conflicting and based on heterogeneous data sources.
Objectives To describe the utilization of topical antipsoriatic drugs among patients with psoriasis in Denmark.
Methods A drug utilization study was performed based on nationwide Danish health registry data. We identified patients who received a first-time hospital diagnosis of psoriasis and redeemed at least one topical drug prescription in the period 2005–2015 (n = 7743). Patients were followed for 3 years from the time of diagnosis. Use of topical and systemic antipsoriatic drugs was described, specified by the type of treatment.
Results The total use of topical drugs was divided between corticosteroids with calcipotriol (31%), calcipotriol (6·5%), very potent corticosteroids (24%), potent corticosteroids (30%), moderate corticosteroids (7·2%) and corticosteroids with antimicrobials (1·6%). There was a 19% reduction in the overall use of topical drugs during the study period. Use increased around the time of diagnosis and the majority of patients redeemed more than two packages of topical drugs during the first year after being diagnosed. Regional differences in patients' use of topical drugs varied considerably. The distribution of use of topical drugs was uneven, with a minority of all patients (25%) using 70% of the total amount of topical treatment. There was a 70% increase in the use of methotrexate over the study period. Biologics were used by up to 6%.
Conclusions The study provides further evidence that the use of topical antipsoriatic drugs shows considerable heterogeneity over time and regional practices, and differences between patients.

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Conflicts of interest
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What's already known about this topic?

- The use of topical drugs for treatment of psoriasis shows considerable heterogeneity worldwide.
- Adherence to topical treatment in patients with psoriasis is low.
- Psoriasis is associated with several comorbidities, such as hypertension, hyperlipidaemia, congestive heart failure, ischaemic heart disease, diabetes mellitus and depression.

What does this study add?

- The use of topical antipsoriatic drugs has decreased, while the use of systemic drugs and biologics has increased.
- The use of topical therapy increases at the time of diagnosis at the hospital clinic and decreases thereafter.

- There is a skewness in the utilization of topical antipsoriatic treatments, with 25% of patients consuming 70% of the topical drugs.

Psoriasis is a chronic autoimmune T-cell-mediated inflammatory skin disease that affects about 2–4% of the adult population in Europe.[1,2] The disease is heterogeneous in morphology, affected sites, age of onset and duration,[3] and presents with large variations in severity of disease, remissions and flare-ups.[4] Psoriasis negatively affects quality of life[5] and causes a substantial social and economic burden both for the patient and for society.[6] Comorbidities linked to psoriasis include hypertension,[7] hyperlipidaemia,[8] congestive heart failure,[9] ischaemic heart disease,[10] diabetes mellitus type 2[11] and depression.[12]

Topical corticosteroids with and without calcipotriol are recommended as first-line treatments in mild-to-moderate psoriasis.[13] Systemic drugs and subsequently biologics are prescribed for more severe psoriasis in which topical therapy and/or phototherapy are less effective.[13] In a recent systematic literature review the worldwide utilization of topical antipsoriatic drugs is described.[14] The study included heterogeneous data sources and study designs, and showed that corticosteroids were used by 16–79% of patients and corticosteroid–calcipotriol combinations by 3·3–71%. Another systematic literature review[15] reported that nonadherence rates to topical corticosteroids in patients with psoriasis (measured by patient-reported adherence rates, weight of medication or data on dispensed medication) ranged from 8% to 88%. In addition, the use of systemic drugs and biologics increased over time after psoriasis diagnosis.[16]

A report of patients' real-life use of antipsoriatic treatments is needed, using nationwide register-based studies reporting from registers that clearly distinguish treatments for psoriasis and include data on the use of topical treatments as well as the use of concomitant treatments. This study aims to address the following five research objectives: (i) to investigate which antipsoriatic drugs are used and to what extent, both over time and on an individual level, in relation to the time of psoriasis diagnosis; (ii) to investigate the occurrence of treatments prescribed for comorbidities associated with psoriasis among patients with psoriasis; (iii) to describe the regional variation in the use of topical antipsoriatic drugs; (iv) to investigate skewness (i.e. a quantification of the extent to which some patients use more topical drugs than other patients) between patients in the use of topical antipsoriatic drugs and (v) to describe the use of systemic drugs and biologics among patients with psoriasis.

Patients and methods

Data sources

National data on drug use in Denmark were extracted from the Danish National Prescription Database.[17,18] The registry contains complete information, from 1 January 1995 onwards, on all prescriptions dispensed to Danish residents at outpatient pharmacies. For the dispensed prescription, the registry contains information on the following variables included in this study: drug type and quantity, date of purchase, and the person's age, sex and region of residence. Registered drugs are categorized according to the Anatomical Therapeutic Chemical classification, a hierarchical classification developed by the World Health Organization for purposes of drug use statistics.[19] The registry is reported to have a high level of completeness and validity.[17]

National data for coding diagnosis and the use of systemic drugs, biologics and phototherapy treatments were extracted from the Danish National Patient Register,[20] which contains nationwide data on all nonpsychiatric hospital admissions since 1977 and outpatient contacts since 1995. Discharge and contact diagnoses were coded according to the International Classification of Diseases (ICD) 8th revision from 1977 to 1993 and ICD 10th revision since 1994. The register contains information on the following variables used in this study: personal identification number, diagnosis and treatment.

Population statistics were obtained and linked by Statistics Denmark, a governmental institution that collects and maintains electronic records from the Danish health registries for a broad spectrum of statistical and scientific purposes. Collected data were linked using a unique identifier assigned to all Danish residents since 1968, which codes sex and date of birth.[21]

The study was approved by the Danish Data Protection Agency and Statistics Denmark's scientific board. According to Danish law, purely register-based studies do not require approval from an ethics committee.[22]

Data selection, procedures and study drugs

We obtained prescription data for all patients aged > 18 years consulting with psoriasis at a hospital dermatology clinic in Denmark during the period from 1 January 2005 to 31 December 2015. Data from each patient were used from 1 year prior to the date on which the patient was diagnosed with psoriasis at a hospital department through to 3 years after the time of diagnosis. To simplify the analyses, and to facilitate the analysis of changes over time, the study period was divided into three arbitrary time periods: 2005–2008, 2009–2012 and 2013–2015.

Several classification systems for topical corticosteroids exist, for example the American Stoughton–Cornell seven-point classification system and a four-point system from the U.K.[23] For the purpose of this study, we divided topical antipsoriatic drugs into six groups: moderate corticosteroids, potent corticosteroids, very potent corticosteroids, corticosteroids in combination with antimicrobials, calcipotriol, and

corticosteroid–calcipotriol combinations (Table 1). All of these drugs are available only via prescription in Denmark and are thus captured by our data sources. To simplify the research questions, some topical drugs were excluded from the data extraction: topical corticosteroid combinations containing salicylic acid and milder corticosteroids (hydrocortisone) were excluded, mainly because these topical drugs are primarily bought over the counter.

We also describe the use of biologics (restricted to etanercept, adalimumab and ustekinumab), systemic drugs (restricted to methotrexate, ciclosporin and acitretin) and phototherapy. Several treatments were not considered: apremilast was not considered in this study, as it was first introduced onto the Danish market in 2015; dimethyl fumarate has limited use and was therefore not considered relevant for this study; and several biologics with marketing authorization for psoriasis in Denmark (i.e. brodalumab, infliximab, ixekizumab and secukinumab) were not included, as these agents did not have a code in the Danish National Patient Register at the time that the data were extracted for the study.

Comorbidities defined by diagnosis or medications prescribed in the year prior to psoriasis diagnosis to treat the comorbidity were considered: hypertension (patients defined by having redeemed a prescription of either a calcium channel blocker, an angiotensin-converting enzyme inhibitor or a thiazide diuretic), hypercholesterolaemia (patients having redeemed a prescription for a statin), congestive heart failure (patients defined by the diagnosis), ischaemic heart disease (patients defined by the diagnosis of acute myocardial infarction), diabetes mellitus type 2 (defined by the use of an oral antidiabetic drug) and depression and anxiety (patients defined as having redeemed a prescription for a selective serotonin reuptake inhibitor).

Table 1 Topical antipsoriatic drugs selected for this study

Drug[a]	ATC class	Drug class description
Clobetasone-17-butyrate	D07AB01	Moderate corticosteroids
Hydrocortisone-17-butyrate	D07AB02	
Betamethasone-17-valerate and betamethasone	D07AC01	Potent corticosteroids
Mometasone furoate	D07AC13	
Fluocinolone acetonide	D07AC04	
Fluocinonide	D07AC08	
Clobetasol propionate	D07AD01	Very potent corticosteroids
Betamethasone and clioquinol	D07BC01	Corticosteroid with antimicrobials
Betamethasone and fusidic acid	D07CC01	
Fluocinolone acetonide and clioquinol	D07BC02	
Calcipotriol	D05AX02	Calcipotriol
Betamethasone, calcipotriol	D05AX52	Corticosteroid with calcipotriol

ATC, Anatomical Therapeutic Chemical. [a]All drugs had a marketing authorization for psoriasis in Denmark in October 2015.

Data analysis

Data were analysed by descriptive statistics. Analysis was divided into questions using data subsets (Table S1; see Supporting Information) and the data were analysed for each of our five research questions. The study population was described by age, sex, Charlson Comorbidity Index[24] and psoriasis comorbidity.

We investigated the amount, distribution and formulation of topical drugs used 1 year prior to vs. 1 year after psoriasis diagnosis and in a 3-year period after psoriasis diagnosis; regional differences in the use of topical drugs compared with the national average; and inequality in the use of topical drugs by the use of Lorenz curves. In Lorenz curves, the *x*-axis represents a given proportion of the population ranked with respect to their use of medication, while the *y*-axis represents the equivalent proportion of the drug use that would be accounted for by the part of the population. By ranking the heavy users first, the depiction of the Lorenz curve returns a concave graph.[25]

Results

Study population

In total, 9332 Danish patients were diagnosed with psoriasis at a hospital dermatology clinic, and during the study period 2005–2015, 7743 Danish patients with psoriasis redeemed at least one topical drug (Table S1). Patients had a median age of 51 years (interquartile range 37–63) and more than half were men (Table 2). Most patients (69–73%) had a low Charlson Comorbidity Index (Table 2), yet a non-negligible proportion of patients had a high Charlson Comorbidity Index (6·3–8·6%) and a considerable proportion (26%) had at least one psoriasis-associated comorbidity (Table 2).

Type of utilized topical antipsoriatic drugs

In total 59 575 prescriptions of topical antipsoriatic drugs had been redeemed (Table S1). The total use during the study period was divided between corticosteroids with calcipotriol (31%), calcipotriol (6·5%), very potent corticosteroids (24%), potent corticosteroids (30%), moderate corticosteroids (7·2%) and corticosteroids with antimicrobials (1·6%). There was a 19% reduction in the total use of all topical drugs during the study period (2005–2008 vs. 2013–2015), caused mainly by a 39% decrease in the use of calcipotriol-containing preparations, while the remaining types of prescribed topical drugs presented only minor fluctuations (Fig. 1a, b). Use during the year before and the year after diagnosis was comparable (Fig. 1c, d). Men aged > 65 years used the most topical drugs, while the distribution in use between sexes was comparable (Fig. S1; see Supporting Information).

Table 2 Baseline characteristics of the patients at the time of psoriasis diagnosis

	North region	Mid region	South region	Capital region	Zealand region
All	n = 348	n = 1734	n = 1843	n = 2842	n = 966
Men	201 (57·8)	911 (52·5)	983 (53·3)	1461 (51·4)	531 (55·0)
Women	147 (42·2)	823 (47·5)	860 (46·7)	1381 (48·6)	435 (45·0)
Age (years), median (IQR)	51·6 (38·7–63·4)	50·5 (36·9–62·9)	50·8 (37·7–62·4)	52·1 (38·0–63·8)	52·2 (38·9–62·6)
CCI[a]					
Low (0)	252 (72·4)	1267 (73·1)	1305 (70·8)	1954 (68·8)	680 (70·4)
Medium (1)	52 (14·9)	261 (15·1)	264 (14·3)	437 (15·4)	145 (15·0)
High (≥ 2)	22 (6·3)	119 (6·9)	158 (8·6)	216 (7·6)	64 (6·6)
Psoriasis-associated comorbidities					
Hypertension[b]	90 (25·9)	380 (21·9)	399 (21·6)	579 (20·4)	194 (20·1)
Hyperlipidaemia[c]	49 (14·1)	224 (12·9)	297 (16·1)	394 (13·9)	126 (13·0)
Congestive heart failure[d]	n < 5	7 (0·4)	9 (0·5)	27 (1·0)	10 (1·0)
Ischaemic heart disease[e]	n < 5	9 (0·5)	10 (0·5)	8 (0·3)	n < 5
Diabetes mellitus type 2[f]	25 (7·2)	110 (6·3)	165 (9·0)	230 (8·1)	79 (8·2)
Depression and anxiety[g]	43 (12·4)	182 (10·5)	147 (8·0)	239 (8·4)	83 (8·6)

Values are given as n (%) unless stated otherwise. IQR, interquartile range. [a]Charlson Comorbidity Index based on diagnoses at any time prior to the index date. Some data were missing. [b]Patients defined by having redeemed a prescription of either a calcium channel blocker, an angiotensin-converting enzyme inhibitor or a thiazide diuretic in the year prior to psoriasis diagnosis. [c]Patients defined by having redeemed a prescription for a statin in the year prior to psoriasis diagnosis. [d]Patients defined by diagnosis in the year prior to psoriasis diagnosis. [e]Patients defined by the diagnosis of acute myocardial infarction in the year prior to psoriasis diagnosis. [f]Patients defined by the diagnosis of type 2 diabetes or having redeemed a prescription for an oral antidiabetic in the year prior to psoriasis diagnosis. [g]Patients defined as having redeemed a prescription for a selective serotonin reuptake inhibitor in the year prior to psoriasis diagnosis.

Many patients increased topical treatment prior to the first contact at the hospital, overall from 45% to 60%. Shortly after the first contact, there was a further 20% increase in use, but this decreased during the years following the first visit. During the following 3-year period, a further decrease was observed leading to a use level similar to that at the time of referral to the hospital (Fig. 2). In the year after diagnosis, 10% of patients did not redeem a second prescription, 23% redeemed two prescriptions, 39% redeemed three to five prescriptions and 28% redeemed more than five prescriptions.

During the study period, a change in the formulation of marketed topical antipsoriatic drugs was observed mainly for corticosteroid and calcipotriol combinations: the use of gel increased from 0·4% to 40% simultaneously with a drop from 100% to 60% in the use of ointment. Moderate corticosteroids were prescribed mainly as cream (84–86%), potent corticosteroids as cream (48–54%), very potent corticosteroids as ointment (46–51%), corticosteroids with antimicrobials as cream (92–97%) and calcipotriol as cream (58–100%) (Table S2; see Supporting Information).

Regional differences in the use of topical antipsoriatic drugs

Considerable regional differences in the use of topical drugs between regions were registered compared with the national average in the 11-year study period. In the period 2012–2015, with regard to the relative difference (of regional vs. national average use), there was an 89% variation in the use of moderate corticosteroids, from highest use in the South region to lowest use in the Zealand region, and a 37% variation in the use of corticosteroids with calcipotriol, with highest use in the Zealand region and lowest use in the South region (Fig. 3). In the remaining period (2005–2012), similar patterns of use were observed, except for fluctuations in the pattern of use of calcipotriol with or without corticosteroids in the North region (Fig. S2; see Supporting Information).

Inequality in the use of topical antipsoriatic drugs

The distribution of the use of topical drugs between patients was moderately skewed for all topical antipsoriatic drug classes, with 25% of patients using 70% of the total amount of the topical drugs (Fig. 4, and Fig. S3; see Supporting Information).

Use of biologics, systemic drugs and phototherapy

The majority of patients did not use antipsoriatic treatments other than topical drugs (Table 3). The biological drug etanercept was used by 0·1% of patients in 2005, increasing to 1·5% in 2010 and then falling to 0·4% in 2015. During the same period, the biological drug adalimumab was used by 1·0% of patients in 2006, 4·4% in 2011 and 1·4% in 2015. The biological drug ustekinumab was introduced onto the Danish market in 2009, when it was used by 0·3% of patients. Its use hereafter increased, with 1·1% of patients using it in 2014.

The use of systemic drugs increased over the study period for methotrexate (74% increase) and acitretin (260%), while

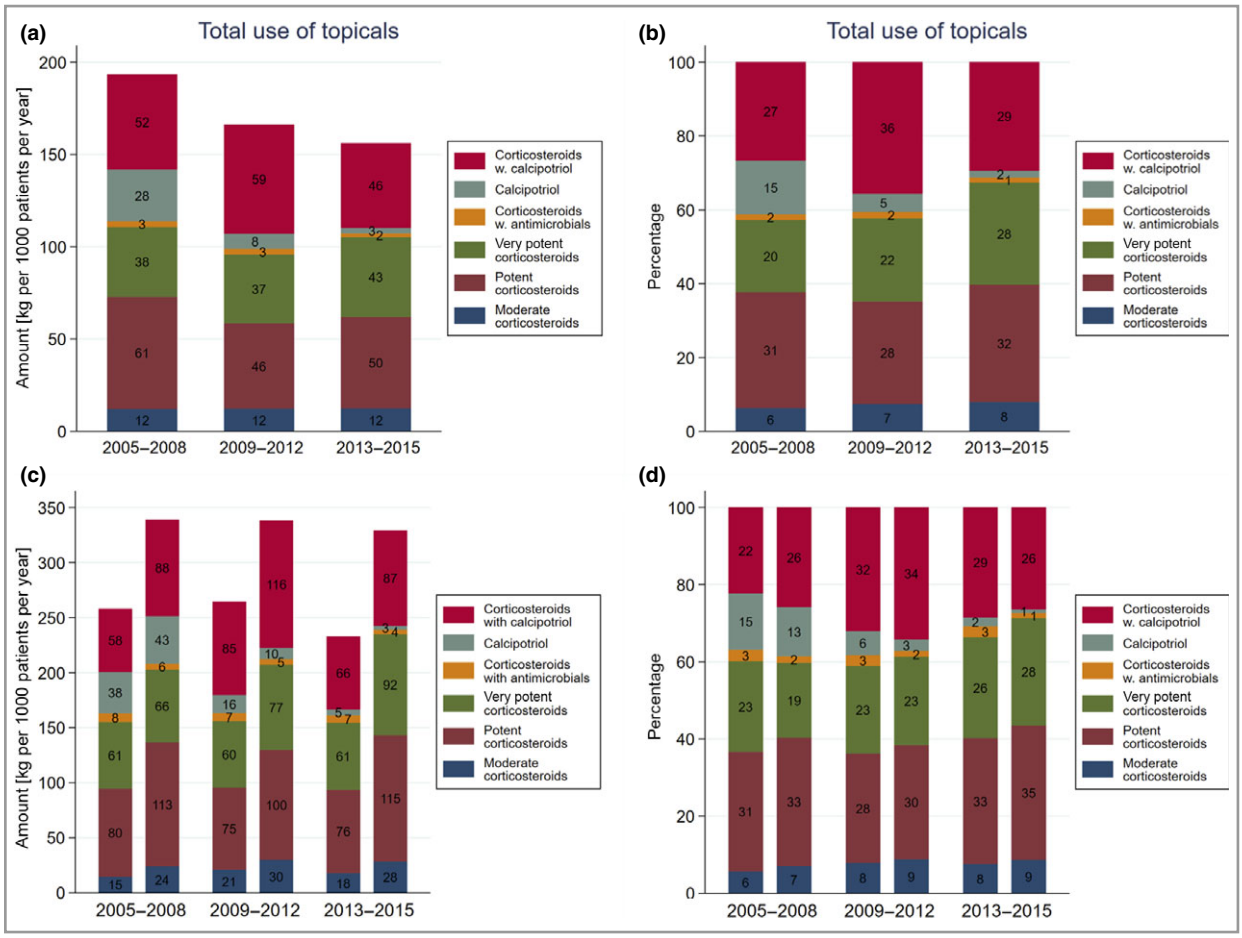

Fig 1. (a) Total use of topical drugs, (b) distribution of use of topicals, (c) total use in the year before (left) and after (right) diagnosis, and (d) distribution of use in the year before (left) and after (right) diagnosis.

ciclosporin use fell by 80% (Table 3). Use of phototherapy treatments fell by 44% (Table 3).

Discussion

Three-quarters of patients used only topical drugs to treat psoriasis, and corticosteroids with calcipotriol or calcipotriol alone were most frequently used. The variation in the use of topical drugs between regions and between individual patients is expected in accordance with the heterogeneous clinical expression of psoriasis. The use of both topical therapies and phototherapy declined, while the use of systemic therapy increased, driven by a 70% increase in the use of methotrexate. Overall, 2·3–6% of patients used biologics during the study period.

The findings from this study are difficult to compare with the varying rates of use of topical corticosteroid-containing antipsoriatic treatments reported in a recent systematic literature review.[14] That review included publications from Western countries using register-based data from national medical care surveys (topical treatments used by 4–77%), claims databases (topical treatments used by 4–42%) and dispensed prescription databases (topical treatments used by 37%). These differences are likely attributable to the marked differences in study designs and study settings, making it difficult to provide a reliable estimate of the real-life use of topical drugs in patients with psoriasis.

The large heterogeneity in how patients use topical drugs[26] does not allow for conclusions regarding adherence; many patients with psoriasis with limited disease may use the same topical drug container for extended periods of time, so drug survival curves (where patients who did not redeem a new prescription within 6 or 12 months are considered nonadherent) must be interpreted with caution.[27] Consequently we refrained from providing a more exact estimate of adherence to topical antipsoriatic drugs.

The 45% increase in the use of topical antipsoriatic drugs around the time of diagnosis at the hospital aligns with previous literature.[28] Patients were treated by a dermatologist in practice or general practitioner before referral to hospital, and the increase could reflect a higher adherence rate when referred to a hospital department or that patients have more severe disease when they are admitted to hospital.

The same types of topical drugs are prescribed by the general practitioner or dermatologist in practice compared with

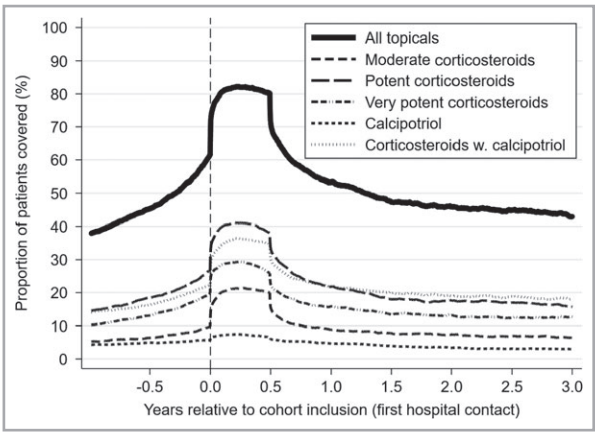

Fig 2. Proportion of patients who redeemed a prescription of topical antipsoriatic drugs within 180 days in relation to the time of hospital diagnosis of psoriasis. Patients were diagnosed with psoriasis at a hospital department at year 0·0. Patients increased use of topical drugs prior to the first contact at the hospital, overall from 45% to 60%. Shortly after the first visit (year 0·0) there was a 20% increase in use followed by a 12% drop 180 days after the first contact. During the following 3-year period, a decrease in use to the level prior to the first hospital contact was registered.

the hospital. The use of topical drugs decreased over time after diagnosis, in accordance with a Nordic register-based study investigating adherence to prescribed topical drugs. Within a year of diagnosis, 88% of patients were nonadherent to the topical drugs, but most patients were prescribed more than one type of topical drug within the first year.[27] Furthermore, three-quarters of patients with psoriasis were on topical therapy only; this either indicates that patients with psoriasis treated at Danish hospitals have limited disease or reflects that patients are undertreated or not treated according to the Danish national guidelines.[13] The decrease in the use of topical drugs may reflect an increased use of methotrexate and a better control of disease. The reduced use of corticosteroids could also reflect increased corticophobia in the psoriasis population or prescribing physicians,[29] or a marked reduction in adherence to prescribed treatments.

The regional differences in the use of corticosteroids probably reflect local traditions and preferences among physicians and were generally found to be stable over time in the regions with larger populations of patients.

The use of methotrexate increased, in accordance with findings from another nationwide study,[30] and complies with the expert recommendation in Denmark, where methotrexate is

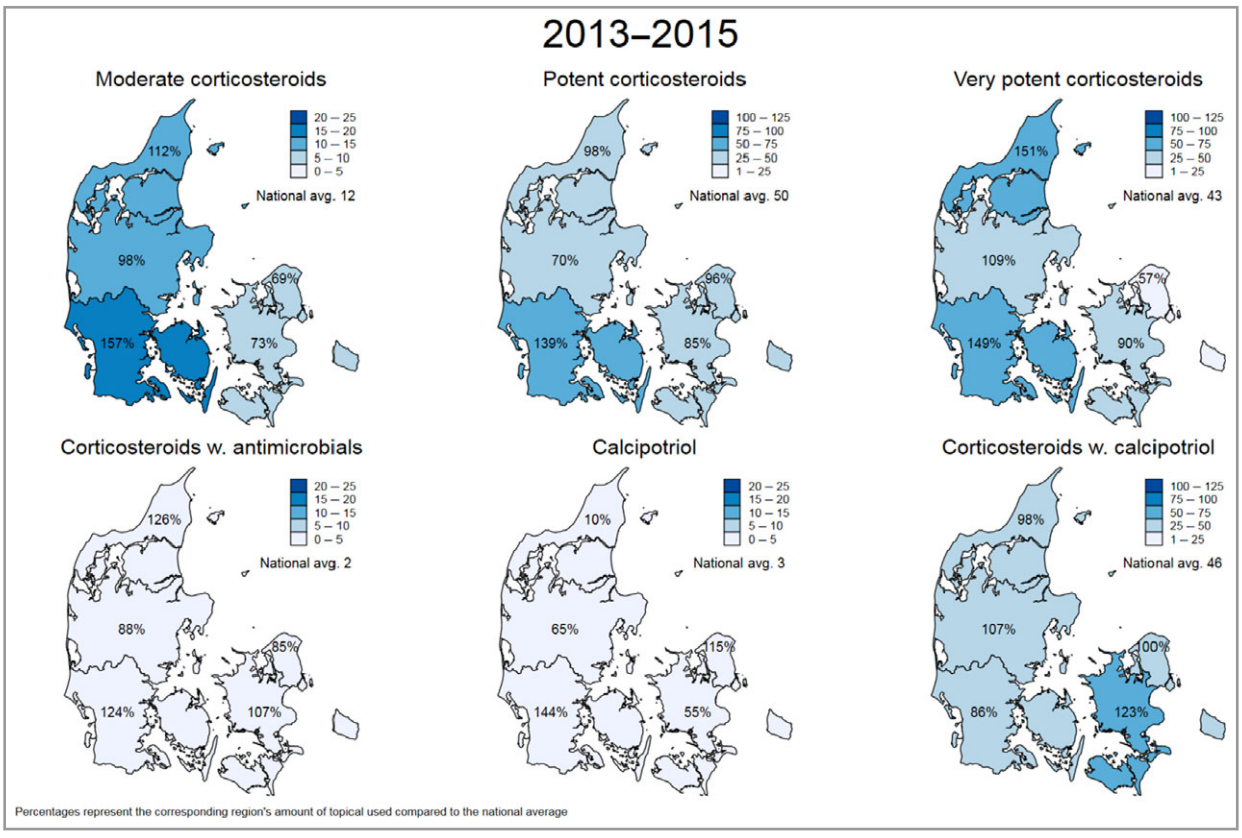

Fig 3. Regional differences in the use of topical antipsoriatic drugs. There were moderate regional differences in the use of topical drugs (from the region with the lowest to the region with the highest use compared with the national average): moderate corticosteroids 88%, potent corticosteroids 69%, very potent corticosteroids 94%, corticosteroids with antimicrobials 41%, calcipotriol 89%, corticosteroids with calcipotriol 37%.

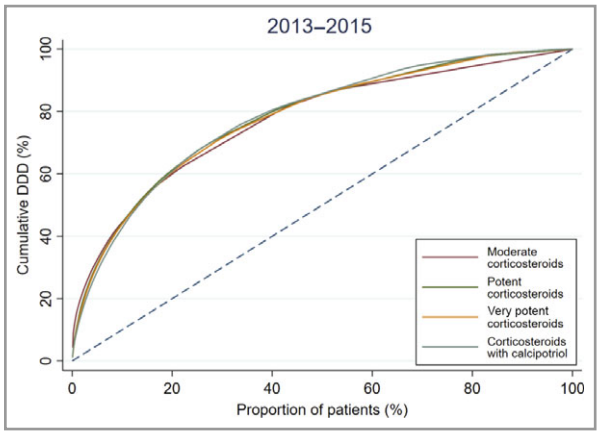

Fig 4. Inequality in overall use during 2013–2015 of the most frequently used topical antipsoriatic drugs: 25% of the patients with psoriasis used 70% of the topical drugs. DDD, defined daily dose.

Table 3 Biologics, systemic drugs and phototherapies prescribed for patients with psoriasis

	Prescribed treatments (%)		
Treatment	2005–2008	2009–2012	2013–2015
None of the treatments below	77·6	70·4	75·0
Biologics			
Etanercept	1·2	2·0	1·1
Adalimumab	1·1	3·8	2·0
Ustekinumab	NA	0·2	0·7
Systemic drugs			
Methotrexate	9·6	17·3	16·7
Ciclosporin	2·0	0·8	0·4
Acitretin	0·5	1·9	1·8
Phototherapy[a]	10·5	9·0	5·9

Treatments were initiated within 1 year of diagnosis. NA, not applicable. [a]Phototherapy includes psoralen combined with ultraviolet A prescribed for the feet, hands and universal; and ultraviolet B phototherapy prescribed in narrowband and broadband.

prescribed at hospitals and by dermatologists in private practice and patients are monitored for adverse events according to national guidelines.[31] Conversely, the use of phototherapy treatments decreased over time, a trend also seen in the U.S.A.,[32] perhaps due to an increasing awareness of potential side-effects and the development of more patient-friendly and less time-consuming treatment alternatives.[33,34]

The fluctuations in the use of biologics may be related to a change in choice of biological treatments in the individual patient due to decreased efficacy over time.[35] Furthermore, in 2009, Denmark established the council for the use of expensive hospital medication RADS (Rådet for Anvendelse af Dyr Sygehusmedicin), and this led to guidelines to ensure that all patients, including patients with moderate-to-severe psoriasis, have equal access to treatment with expensive hospital medications.[36] RADS provided the first version of recommendations for psoriasis in 2012, where both ustekinumab and adalimumab were recommended as first-line treatment,[37] as reflected in this study. With the increasing cost of biologics and the introduction of biosimilars, treatment decisions are evidently becoming more centrally regulated and less physician dependent.[38,39]

The essential strength of this study is the use of real-life data from the Danish registries, with their high level of completeness and validity.[18]

A main limitation of this study is the lack of clinical data on scoring and monitoring the severity of psoriasis in the patients with psoriasis included, which could have provided valuable information on the interplay between temporal changes in the severity of psoriasis and the use of medication. The data presented must be interpreted with the background information that Danish patients are reimbursed for drug expenses depending on annual consumption and choice of drug. For example, topical corticosteroids with antimicrobials are not reimbursed, which may to some extent explain their limited use. Biologics are provided by the hospital free of charge. Some biologics not coded in the Danish National Patient Register, such as infliximab, have been used in the treatment of psoriasis.

The high use of calcipotriol–corticosteroid preparations observed in the North region in 2009–2012 may reflect that only a few patients from the North region were included in the study, and only a few dermatologists in practice with a certain prescription pattern treated these patients. The study comprised only patients diagnosed at hospital clinics, including a majority of patients manageable on topical drugs, and also patients with more severe psoriasis not amenable to recommended first-line treatments.

In conclusion, the use of topical antipsoriatic drugs varies in individual patients and reflects that psoriasis is heterogeneous in severity and development over time. The use of topical drugs is influenced by traditions among physicians. However, prescription patterns in Denmark are similar among general practitioners, dermatologists in practice and hospital clinics. The largest amount of topical antipsoriatic drugs is used around the time of hospital diagnosis.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig S1. Use of topical antipsoriatic drugs divided by age and sex.

Fig S2. Regional differences in use of topical antipsoriatic drugs.

Fig S3. Inequality in use of topical treatments.

Table S1 Description of the different data subsets used.

Table S2 Use of formulations of topical antipsoriatic drugs.