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Systemic therapy and the use of complementary and alternative medicine in patients with recognized occupational hand eczema in Denmark: A cross-sectional questionnaire-based study

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Funding information

The Danish Working Environment Research Fund (Arbejdsmiljøforskningsfonden) and The Health Foundation (Helsefonden)

Abstract

Background: Concerns have been raised that a chronic course of hand eczema (HE) could be fostered by a lack of efficient treatment at an early stage.

Objectives: First, to assess the prevalence of systemic treatment in patients with chronic occupational HE (OHE) and relate this to demographic data, HE severity, and atopic dermatitis (AD). Second, to explore the use of complementary and alternative medicine (CAM) in the same population.

Methods: Baseline data were obtained from a registry-based study including patients with recognized OHE in a 2-year period in Denmark, comprising a total of 2703 workers. A follow-up questionnaire after 4 to 5 years included questions on disease severity and treatments.

Results: A total of 1565 participants responded to the questionnaire, and of these 1203 had ongoing HE at follow-up and were included in the study. In total, 10.0% had received systemic therapy, whereas this share was 13.3% in those with self-reported moderate-to-severe HE. Age >35 years, previous or current AD, and severe eczema were factors related to use of systemic treatment. Use of CAM was reported by 6.2% of the study population.

Conclusions: We suggest that chronicity of HE may be perpetuated by the lack of efficient treatment.

KEYWORDS

chronic eczema, hand eczema, occupational hand eczema, systemic treatment, treatment of hand eczema, wet work

1 | INTRODUCTION

Hand eczema (HE) is a common skin disease in the general population with an incidence of 3.3 to 8.8 per 1000 person-years.¹ Occupational hand eczema (OHE) is a frequently recognized occupational disease in Denmark,² affecting mainly young individuals with a mean age of 36 years.³ OHE is recognized in Denmark if the eczema is diagnosed by a doctor and caused or aggravated by

occupational exposures.² There is a high risk of the eczema taking a chronic course. In a Swedish study, after 12 years of follow-up, about 70% of patients with OHE were still having symptoms.⁴ It is estimated that 5% to 7% of patients with HE have chronic HE and 2% to 4% of these are estimated to be refractory to topical treatment.⁵ Risk factors related to a poor prognosis are high age, wet work, lower socioeconomic status, and a history of atopic dermatitis (AD).^{6,7}

It has been suggested that a lack of efficient treatment among patients with HE may promote chronicity. Contributing factors may include not seeking, or delaying to seek, medical treatment, and doctors not prescribing effective treatment in the initial stages of the disease (patient's and doctor's delay, respectively).⁸ At the same time, a lack of efficient treatment may also encourage the use of complementary and alternative medicine (CAM).

While some patients with HE can be successfully treated by topical treatment or UV therapy, others are recalcitrant to these treatments and systemic therapy may then be needed to obtain disease control.^{9,10}

To better elucidate whether a lack of efficient treatment may promote chronicity and possibly encourage use of CAM, more data on treatment of patients with HE are needed. The primary aim of this study was to investigate which treatments are being offered to patients with chronic OHE in Denmark, with a focus on systemic therapy, and relate this to demographic data as well as disease-related variables. A secondary aim was to explore the use of CAM in the same population.

2 | METHODS

The study is a register-based cohort study in Denmark including 2703 patients aged 18 years or older with recognized OHE within a 2-year period (January 2010 to December 2011). We excluded patients without eczema at follow-up and included only those who had ongoing HE in the last 12 months, finally including 1203 patients in this study. Data such as demographic information (age at onset, gender), history of AD, diagnosis, and profession at the time of notification were obtained from files in the Danish Labour Market Insurance.

Patients were defined as having AD if they had a current or previous medical history of AD registered in the statements from specialists in dermatology or medical files. Based on profession, patients were divided into five education groups: unskilled profession, skilled profession, higher education for 1 to 3 years, higher education for 3 to 4.5 years, and higher education for 5 years or more. A follow-up questionnaire was sent to participants in 2015, that is, 4 to 5 years after recognition of occupational eczema. The questionnaire included questions regarding status of HE, conventional treatment, alternative treatment, and if the patients were worried about side effects of treatments.

Patients were asked whether they had used systemic treatment at the time of the questionnaire or when their HE was at its worst. A list of medications to choose from included methotrexate, azathioprine, acitretin, alitretinoin, mentioning brand names of the products, and "other," which offered the chance to write the name of the treatment (Table 1). Questions about the use of calcineurin inhibitors were not included. An open question was used for asking about the use of CAM, and answers comprised use of acupuncture, homeopathy, green tea, vinegar, salt water, light therapy, fish pedicure, and cannabis oil. Chronic HE was defined as eczema lasting for more than 3 months or occurring at least two times a year.¹¹ Self-rated severity was assessed using a questionnaire, in which patients rated the current severity of HE on a scale from 0 (clear) to 10 (worst; taken from the Nordic Occupational Skin Questionnaire-2002 [NOSQ-2002] question¹²), and

TABLE 1 Distribution of systemic treatment expended by the study population

Treatments	Total number
Methotrexate	53
Azathioprine	40
Acitretin/Alitretinoin	36
Prednisolone	15
Cyclosporine	5
Mycophenolate mofetil	1

Note: The total number of patients receiving systemic treatment was 117. Some patients had received more than one treatment. A total of 87 patients had received only one systemic treatment, and 21 had received two types of systemic treatment and nine had received three or more types of systemic treatment.

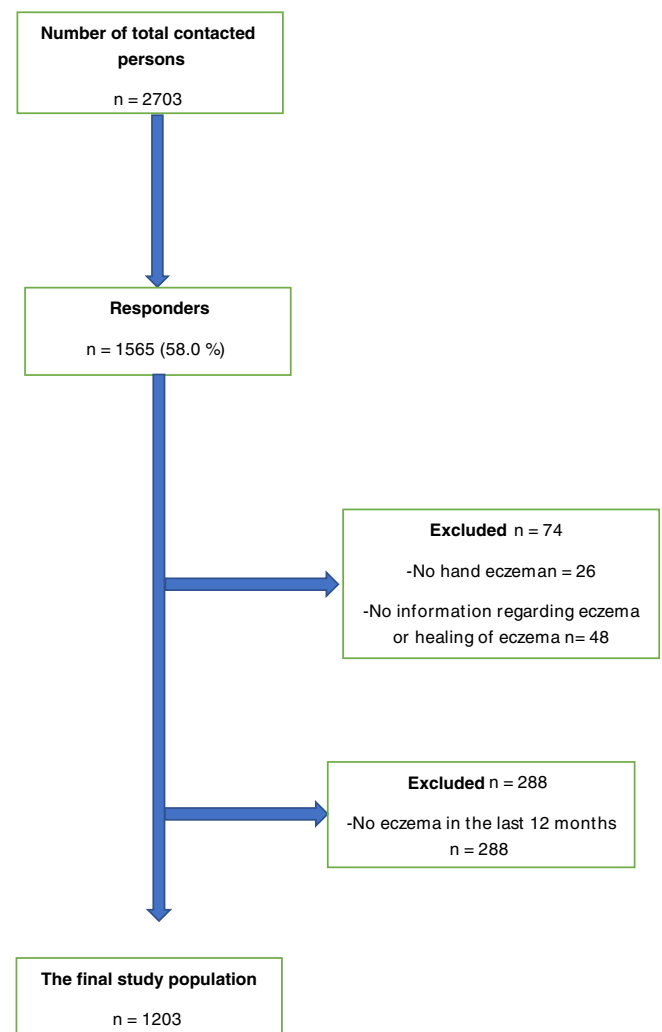


FIGURE 1 STROBE flow diagram: selection of the study population. All patients aged 18 years or older with recognized occupational eczema according to the Danish Labour Market Insurance. The data were from January 2010 to December 2011. In the study period, 2730 patients had recognized occupational eczema, among which 2703 patients were available for follow-up and 1565 responded to the questionnaire

severity was defined as mild (0-4) and moderate to severe (5-10). Further details about the study are found in a previously published article.¹³

We used logistic regression analysis to examine the association between being treated with systemic and alternative therapy and age group, gender, having AD, educational level, eczema severity,

geographic region, and having concerns about side effects of the treatment. Odds ratio (OR) are given, adjusted for all the baseline characteristics such as age group, gender, having AD, educational level, eczema severity, geographic region, and having concerns about side effects of the medication. Statistical analysis was performed with SAS ENTERPRISE GUIDE 7.1 (SAS, Cary, North Carolina).

TABLE 2 The association between being treated with systemic treatment and age, gender, atopic dermatitis, educational level, eczema severity, geographic region, and concern about side effects of the treatment

	Total	Systemic treatment	Nonsystemic treatment	Crude odds ratio (95%CI) ^a	Adjusted odds ratio (95%CI) ^b	P-value adjusted ^c
Number of included patients, n (%)	1175 ^d	117 (10.0)	1058 (90.0)			
Age group (y)						
18-25	251	14 (5.6)	237 (94.4)	1	1	<.01
26-35	320	23 (7.2)	297 (92.8)	1.31 (0.66-2.60)	1.80 (0.85-3.79)	
36-45	256	31 (12.1)	225 (87.9)	2.33 (1.21-4.50)	3.31 (1.61-6.83)	
46-55	240	37 (15.4)	203 (84.6)	3.09 (1.62-5.87)	4.62 (2.23-9.57)	
≥56	108	12 (11.1)	96 (88.9)	2.12 (0.94-4.74)	3.65 (1.50-8.89)	
Gender						
Men	299	26 (8.7)	273 (91.3)	1	1	.42
Women	876	91 (10.4)	785 (89.6)	1.22 (0.77-1.92)	1.22 (0.75-1.98)	
Atopic dermatitis						
No	872	78 (8.9)	794 (91.1)	1	1	<.01
Yes	303	39 (12.9)	264 (87.1)	1.50 (1.00-2.26)	2.14 (1.32-3.45)	
Educational level						
Unskilled profession	331	38 (11.5)	293 (88.5)	1	1	.09
Skilled profession	619	68 (11.0)	551 (89.0)	0.95 (0.62-1.45)	1.00 (0.64-1.56)	
Higher education 1-3 y	20	2 (10.0)	18 (90.0)	0.86 (0.19-3.84)	0.68 (0.14-3.22)	
Higher education 3-4.5 y	173	8 (4.6)	165 (95.4)	0.37 (0.17-0.82)	0.37 (0.16-0.84)	
Higher education ≥5 y	32	1 (3.1)	31 (96.9)	0.25 (0.03-1.88)	0.25 (0.03-1.90)	
Severity (now) ^e						
Mild	646	46 (7.1)	600 (92.9)	1	1	
Moderate to severe	512	68 (13.3)	444 (86.7)	2.00 (1.35-2.96)	1.80 (1.19-2.73)	<.01
Geographic region ^f						
Capital region of Denmark	315	28 (8.9)	287 (91.1)	1	1	.56
Region Zealand	176	19 (10.8)	157 (89.2)	1.24 (0.67-2.29)	1.24 (0.66-2.34)	
Region of Southern Denmark	221	20 (9.0)	201 (91.0)	1.02 (0.56-1.86)	0.90 (0.47-1.71)	
Central Denmark region	337	38 (11.3)	299 (88.7)	1.30 (0.78-2.18)	1.42 (0.83-2.43)	
North Denmark region	116	10 (8.6)	106 (91.4)	0.97 (0.45-2.06)	1.01 (0.46-2.21)	
Concern about side effects of medical treatment ^g						
No concern	394	21 (5.3)	373 (94.7)	1	1	<.01
Little concern	542	59 (10.9)	483 (89.1)	2.17 (1.30-3.64)	1.98 (1.15-3.41)	
Strong concern	161	37 (23.0)	124 (77.0)	5.30 (2.99-9.40)	4.47 (2.44-8.19)	

Note: The estimates highlighted in bold are with P-values <.05.

^aLogistic regression.

^bLogistic regression. Adjusted for age group, gender, having or having had atopic dermatitis, educational level, eczema severity, and geographic region.

^cP-value adjusted for age group, gender, having or having had atopic dermatitis, educational level, eczema severity, and geographic region.

^dThere are 28 missing questions on treatment.

^eThere are 17 missing questions on severity.

^fThere are 10 missing questions on geographic region.

^gThere are 78 missing questions on concern.

3 | RESULTS

In the study period, 2730 patients had recognized occupational eczema according to the Danish Labour Market Insurance and 2703 patients were available for follow-up.¹³ Response was 58%

(1565 respondents). For more detailed information see a previous publication.¹³ We excluded 362 patients: 26 patients did not have HE (these had eczema elsewhere on the body), 48 patients did not have information regarding healing of eczema, and 288 patients reported at follow-up not to have had HE within the last

TABLE 3 The association between being treated with complementary and alternative medicine and age, gender, atopic dermatitis, educational level, eczema severity, geographic region, and concern about side effects of the treatment

	Total	Alternative treatment	No alternative treatment	Crude odds ratio (95%CI) ^a	Adjusted odds ratio (95%CI) ^b	P-value ^c
Number of included patients, n (%)	1174 ^d	73 (6.2)	1101 (93.8)			
Age group (y)						
18-25	251	22 (8.8)	229 (91.2)	1	1	.41
26-35	319	19 (6.0)	300 (94.0)	0.66 (0.35-1.25)	0.86 (0.43-1.75)	
36-45	254	19 (7.5)	235 (95.5)	0.84 (0.44-1.60)	1.16 (0.58-2.32)	
46-55	242	9 (3.7)	233 (96.3)	0.40 (0.18-0.89)	0.51 (0.21-1.23)	
≥56	108	4 (3.7)	104 (96.3)	0.40 (0.14-1.19)	0.68 (0.22-2.17)	
Gender						
Men	298	12 (4.0)	286 (96.0)	1	1	.10
Women	876	61 (7.0)	815 (93.0)	1.78 (0.95-3.36)	1.74 (0.90-3.37)	
Atopic dermatitis						
No	870	42 (4.8)	828 (95.2)	1	1	.01
Yes	304	31 (10.2)	273 (89.8)	2.24 (1.38-3.63)	1.98 (1.15-3.42)	
Educational level						
Unskilled profession	336	22 (6.6)	314 (93.4)	1	1	.96
Skilled profession	614	40 (6.5)	574 (93.5)	1.00 (0.58-1.70)	1.00 (0.57-1.76)	
Higher education 1-3 y	20	2 (10.0)	18 (90.0)	1.59 (0.35-7.28)	0.88 (0.11-7.19)	
Higher education 3-4.5 y	173	9 (5.2)	164 (94.8)	0.78 (0.35-1.74)	0.73 (0.31-1.73)	
Higher education ≥5 y	31	0 (0.0)	31 (100.0)	–	–	
Severity (current) ^e						
Mild	645	28 (4.3)	617 (95.7)	1	1	<.01
Moderate to severe	511	41 (8.0)	470 (92.0)	1.92 (1.17-3.15)	2.05 (1.22-3.43)	
Geographic region ^f						
Capital region of Denmark	315	15 (4.8)	300 (95.2)	1	1	.24
Region Zealand	177	10 (5.7)	167 (94.4)	1.20 (0.53-2.73)	1.21 (0.53-2.79)	
Region of Southern Denmark	223	15 (6.7)	208 (93.3)	1.44 (0.69-3.02)	1.09 (0.49-2.43)	
Central Denmark region	334	19 (5.7)	315 (94.3)	1.21 (0.60-2.42)	1.15 (0.56-2.37)	
North Denmark region	115	12 (10.4)	103 (89.6)	2.33 (1.06-5.14)	2.46 (1.08-5.58)	
Concern about side effects of medical treatment ^g						
No concern	392	9 (2.3)	383 (97.7)	1	1	<.01
Little concern	542	39 (7.2)	503 (92.8)	3.30 (1.58-6.89)	2.54 (1.19-5.41)	
Strong concern	160	23 (14.4)	137 (85.6)	7.14 (3.23-15.82)	5.76 (2.49-13.35)	

Abbreviation: CI, confidence interval.

^aLogistic regression.

^bLogistic regression adjusted for age group, gender, having or having had atopic dermatitis, educational level, eczema severity, geographic region, and having a concern.

^cP-value adjusted for age group, gender, having or having had atopic dermatitis, educational level, eczema severity, and geographic region.

^dThere are 29 missing questions on alternative treatment.

^eThere are 18 missing questions on severity.

^fThere are 10 missing questions on geographic region.

^gThere are 80 missing questions on concern.

12 months. The final study population comprised 1203 patients (Figure 1).

With respect to the use of moisturizers, 787 (65.6%) reported its use on a daily basis, whereas 290 (24.2%) patients did not use moisturizers at all (four answers missing). Regarding topical corticosteroids, 979 patients (83.3%) reported periods with daily use of these, whereas 196 (16.7%) did not use them at all (28 answers missing). From 1175 patients included in the study (28 missing answers), 117 received systemic therapy. UV therapy was also used in this group by 55, and by 256 patients without previous use of systemic treatment.

Five hundred and twenty four patients reported moderate-to-severe HE at the time of the questionnaire. Of these 94 (17.9%) were aged 18 to 25 years, 132 (25.2%) were 26 to 35 years, 124 (23.7%) were 36 to 45 years, 123 (23.5%) were 46 to 55 years, and 51 (9.7%) were older than 55 years (missing = 20). In the group reporting moderate-to-severe HE, 162 (30.9%) had an unskilled profession, 289 (55.1%) were an skilled profession, three (0.6%) had a higher education of 1 to 3 years, 57 (10.9%) had a higher education of 3 to 4.5 years, and 13 (2.5%) had a higher education of more than 5 years (missing = 20). AD according to our criteria was seen in 121 (23.1%) patients reporting moderate-to-severe HE. Of the ones who had rated their eczema 9 or 10 on a visual analog scale, 7.9% had reported receiving or having received systemic treatment. Of the 288 patients without self-reported HE in the last 12 months, 14 (5.0%) reported having received systemic treatment at some point.

Distribution of agents used for systemic treatment is shown in Table 1, and the association between treatment and age, sex, AD, educational level, eczema severity, geographic region, and concern about side effects of the treatment is presented in Table 2. Of the 36 patients who reported treatment with acitretin/alitretinoin, one had a history of psoriasis. The age groups 36 to 45 years, 46 to 55 years, and older than 55 years were more likely to receive or having received systemic treatment than the younger age groups (Table 2). Patients with a history of AD according to our criteria were significantly more likely to receive systemic treatment than those without AD (adjusted OR 2.14 [95% confidence interval (CI): 1.32-3.45]). This also applied to those with moderate-to-severe HE compared with those with mild HE (adjusted OR 1.80 [95%CI: 1.19-2.73]; Table 2). Educational level, gender, or geographic region was not markedly related to systemic therapy. Patients with higher education of 3 to 4.5 years were less likely to receive systemic treatment. Proportionately more patients who received systemic treatment were concerned about side effects of the medication (Table 2).

Characteristics of the study population regarding CAM are given in Table 3. A total of 73 (6.2%) patients were using or had used CAM. Patients with a history of AD were significantly more likely to receive CAM (adjusted OR 1.98 [95%CI: 1.15-3.42]), as were those from the North Region of Denmark (adjusted OR 2.46 [95%CI: 1.08-5.58]). No significant associations were found regarding gender, age, and educational level; however, a significant statistical association between severity of HE and use of CAM was found (Table 3). CAM users had greater concerns about the side effects of traditional medical therapy

as compared with those not using CAM (adjusted OR 5.76 [95%CI: 2.49-13.35]; Table 3). Sixteen of 117 (13.7%) who received systemic therapy also used CAM, whereas only 56 (5.3%) of the 1048 who had not received systemic treatment reported the use of CAM (missing 10).

4 | DISCUSSION

A main finding of this study is that only 10.0% of the total study population, and 13.3% of those with moderate-to-severe self-reported HE, had received systemic therapy. This may indicate that systemic therapy is underutilized in this particular population, which comprises patients with ongoing OHE at 4-5 years follow-up.

A German study investigated medical care among 1163 chronic HE patients and reported the number of patients receiving systemic therapy (including corticosteroids but excluding antihistamines) to be 35%.¹⁴ The noticeably higher percentage in that study compared with our data may be due to the fact that patients from specialized centers were over-represented, whereas in our study only patients with notified OHE in Denmark were included. Differences in legal and medical system between Germany and Denmark may also have had an impact on these results. A 5-year follow-up study from Germany reported that 39.0% of study population had received systemic therapy (alitretinoin, acitretin or methotrexate), whereas in our study this was the case for only 10%.¹⁵ In Denmark, the only drug registered for systemic treatment of chronic HE is alitretinoin, which can be reimbursed only if the treatment with one previous systemic drug has failed and this naturally influences the results of our study. Off-label treatments used comprise azathioprine, methotrexate, ciclosporine, acitretin, and mycophenolate mofetil. Systemic steroids are not recommended for long-term use in most guidelines. In our study a surprisingly low number of patients (only 15) reported treatment with systemic steroids, which may be explained by the fact that patients were not asked directly about treatment with steroids. Instead, they could write the treatment under "other treatments." Another difference between the two studies is that in the German study severity of HE was physician as well as patient assessed,¹⁵ whereas we only used self-reported severity on a 10- point scale. However, all patients included had had continuous, chronic OHE for more than 4-5 years. The assumption that the low percentage of systemically treated patients may be due to physicians not taking HE seriously is supported by previous findings in a study from the United States, which investigated prevalence and initial treatment of HE and reported that 62% of newly diagnosed patients with HE were not prescribed any treatment in the first 12 months after diagnosis.¹⁶ Another possible explanation of the low percentage of patients who had received systemic therapy could be that the disease was considered too mild by the physicians. However, even among those patients who had rated their eczema 9 or 10 on a visual analog scale, only 7.9% had received systemic therapy.

Numerous reasons may account for the possible underutilization of systemic treatment in HE patients, and the explanation may lie with the patient as well as with the physician.¹⁷ We identified the use of

systemic treatment associated with increasing age, probably due to an increased risk of development of chronic HE with increased age, as well as a reluctance among physicians to initiate systemic treatment in younger age groups. Increased use of systemic treatment in patients with previous or current AD is not surprising, because these patients are probably more familiar with medical treatments and long-lasting eczema. An additional possible bias is that in some patients the treatment could have been given for the generalized AD and not specifically for HE.

We found that patients with higher education of 3 to 4.5 years were less likely to receive systemic treatment compared with other groups. A possible explanation for this difference could be that 94% of the patients in this group were women and 40% in this group were aged between 26 and 35 years. These women are of childbearing age and even if this is not a contraindication for systemic treatment, this needs, however, to be carefully considered in the selection of the agent and monitoring of the treatment. Most patients included in our study were women and this is related to the fact that in Denmark two-thirds of people with recognized OHE are women³ unlike in Germany where gender differences are small with respect to OHE.^{18,19} Moisturizers were not used by 24 (2%) of the patients in this study. This is a surprisingly high percentage as moisturizers constitute the baseline therapy for HE.

The percentage of HE patients using CAM in this study was 6.2%, which is remarkably low, in contrast to other dermatological diseases such as psoriasis (up to 60%)²⁰⁻²² and AD (51%).²⁰ This could partly be explained by the questionnaire using an open question regarding CAM, and some CAM treatments – not recognized by the patients as CAM – may not have been reported. Furthermore, results are based on small numbers and may be underpowered. AD and severe eczema were variables associated with CAM use, which has been reported before²⁰⁻²² (Table 3). Although more people with AD used CAM, it is still a small number of patients. At the same time this contains a wide variety of treatments reported in the CAM group. AD patients may also have a long duration of eczema persisting since childhood, giving them a longer time frame of living with the eczema and thereby more years to seek other treatments.

With respect to geographic differences, patients from the northern region of Denmark, which has a larger rural population, were significantly more likely to use CAM, which is in line with previous findings that patients from town/rural districts report more frequent use of CAM than patients from capital city areas.²³ However, this statistical association might be just due to chance, because this group represented only small number of cases.

CAM users were more concerned about side effects of medical treatment, which could indicate that the CAM of choice is believed to have fewer side effects, which underlines the need for information in the treatment process. In this study patients who received systemic treatment were more likely to use CAM compared with those who did not receive (13.7% vs 5.3%), which could indicate that CAM use would not be an alternative for systemic treatment, but only another option for treatment in those in whom systemic treatment did not solve the problem. Patients' concern about side effects should be

taken seriously because it might affect treatment adherence to traditional treatment in a negative direction.

The strength of the study is the follow-up design of a relatively large group of HE patients. However, our data should be interpreted with caution due to typical limitations of a cross-sectional questionnaire-based design. We know from previous studies that self-reported data often differ from physician-based data,²⁴ and furthermore, there might be gender-specific bias, because eczema is often perceived as worse by women compared with men.²⁵ A limitation of this study is that the number of patients being offered a prescription for systemic treatment, but not redeeming it, is unknown, so we cannot differentiate between doctors' and patients' hesitation to use systemic treatment. Another possible drawback to the study is the small number of patients who had received CAM. A potential bias to our data is the fact that data on severity are self-reported.²⁴ Moreover, we do not have data for the whole period between recognition of OHE in 2010/2011 and the questionnaire in 2015. Information about medication was self-reported and not retrieved from a register, which may also be considered as a limitation. Because the aim of this study was to investigate use of systemic treatment in patients with chronic HE, 288 patients were excluded because they did not have HE at follow-up. However, among those only 5.0% had received systemic treatment at some point, which is even fewer than those in the group with chronic HE patients.

In conclusion, the use of systemic therapy in our study on patients with occupational chronic HE in Denmark was low, indicating that systemic treatment might be insufficiently used. This fact could be an important factor leading to chronicity of HE, and should be discussed at a political level.

CONFLICTS OF INTEREST

None declared.

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How to cite this article: Barati Sedeh F, Ebbelhøj NE, Agner T, Carøe TK. Systemic therapy and the use of complementary and alternative medicine in patients with recognized occupational hand eczema in Denmark: A cross-sectional questionnaire-based study. *Contact Dermatitis*. 2020;1-7. <https://doi.org/10.1111/cod.13477>