Depression, Anxiety, Health Care Costs, and Utilization among Patients with Hyperhidrosis in a Real-World Database Analysis

M. Hull,[1*] K.K. Gillard,[2] J. Peterson-Brandt,[1] S.Z. Klein[3]

[1]OptumInsight Life Sciences, Eden Prairie, MN, USA; [2]Dermira, Inc., a wholly-owned subsidiary of Eli Lilly and Company, Menlo Park, CA, USA; [3]University of Utah Hospital, Salt Lake City, UT, USA

*Michael Hull was an employee of Optum at the time the study was conducted

INTRODUCTION

- Hyperhidrosis is a chronic medical condition characterized by excess sweat production beyond that which is necessary to maintain thermal homeostasis, affecting an estimated 4.8% of the United States (US) population[1]
- The condition has reportedly been associated with impacts on health-related quality of life, social and emotional stress, and a relatively high risk of concomitant depression and anxiety[2-5]
- Real-world observational data are limited in patients with hyperhidrosis, suggesting that additional research is warranted

OBJECTIVES

- To describe clinical characteristics and treatment patterns of patients with hyperhidrosis
- To determine the prevalence of depression and anxiety among patients with hyperhidrosis relative to patients in a control cohort
- To examine health care resource utilization (HCRU) and costs associated with concomitant depression and/or anxiety in patients with hyperhidrosis

METHODS

Patient Selection

- Patients were identified from January 2010 through November 2017 from the Optum Research Database, a de-identified database that contains medical and pharmacy information for commercial and Medicare Advantage claims
- Inclusion criteria for patients newly diagnosed with hyperhidrosis were
  - Commercial health plan members with continuous enrollment with medical and pharmacy coverage for 12 months before (the baseline or pre-index period) and ≥12 months after the index date (follow-up period)
  - ≥2 hyperhidrosis diagnosis codes and/or prescription claims for extra- or prescription-strength antiperspirant; the index date was the first observed claim indicating hyperhidrosis
  - No claims for medical procedures (botulinum toxin A, microwave thermolysis, suction curettage, iontophoresis, endoscopic thoracic sympathectomy) with codes specific to hyperhidrosis treatment during the baseline period
  - No claims for the above medical procedures or pharmacy claims for oral systemic therapies not specific to hyperhidrosis treatment within 7 days of the index date
- Patients in the hyperhidrosis cohort were followed for a variable period of ≥12 months
- A control cohort (CC) was constructed with comparable index year, age, gender, and health plan region to the hyperhidrosis cohort, and had the following key inclusion criteria
  - No evidence of hyperhidrosis based on medical claims or pharmacy claims for prescription-strength antiperspirants
  - Continuous enrollment criteria identical to that of the hyperhidrosis cohort
- The index date for control cohort patients was selected as a random date of health care resource utilization during the identification period, such as an office visit, inpatient admission, or a prescription claim; patients were followed for a fixed 12-month period beginning on the index date

Outcomes

- Outcome variables were
  - Index year, age, gender, and geographic region
  - Baseline comorbid conditions, defined using indicator variables for specific disease conditions based on International Classification of Disease (ICD)-9-CM and ICD-10 diagnoses employed by the Clinical Classifications Software, managed by the Agency for Healthcare Research and Quality
  - Hyperhidrosis treatments (hyperhidrosis cohort only, variable follow-up period)
    - These were determined by claims made during a variable follow-up period for prescription-strength antiperspirants, botulinum toxin A injections, oral systemic therapies, microwave thermolysis, suction curettage, iontophoresis, endoscopic thoracic sympathectomy, and/or glycopyrronium cloth
  - Proportion of days covered (PDC), a measure of adherence to chronic medications (hyperhidrosis cohort only)
    - PDC was calculated for the first 12 months of follow-up by dividing the number of days on which medication was available based on filled prescriptions by the number of days between the earliest prescription claim in the observation period through the end of the observation period (i.e., twelve months of follow-up)
  - Depression and/or anxiety claims (hyperhidrosis and control cohort, 12-month follow-up period)
    - Depression was defined as ≥1 medical claim with a diagnosis code for depression in any position and/or ≥1 pharmacy claim for a medication indicated specifically as an antidepressant
    - Anxiety was defined as ≥1 medical claim with a diagnosis code for anxiety in any position and/or ≥1 pharmacy claim for a medication indicated specifically as an anxiolytic
    - Depression and/or anxiety was defined as above while also including patients without a diagnosis code for depression or anxiety but with ≥1 pharmacy claim for a medication indicated for the treatment of both depression and anxiety
    - Second indicator variables identified patients with new depression, anxiety, and depression and/or anxiety (claims that were not identified during the pre-index period)
  - All-cause HCRU within the hyperhidrosis cohort; patients with ≥1 ambulatory visit, ≥1 emergency department (ER visit), or ≥1 inpatient stay during follow-up were identified, and each type of encounter was counted
  - All-cause health care costs within the hyperhidrosis cohort, calculated as combined health plan and patient paid amounts; costs were inflation-adjusted to 2018 dollars using the annual medical care component of the Consumer Price Index

Analysis

- All variables were analyzed descriptively
- The occurrence, counts, and time until treatments were summarized; to account for variable follow-up, binary indicators of treatments and counts of the number of treatments were also presented as incidence rates, with rates per person-year, the number of events (i.e., patients who had the treatment), and the number of person-years; a Kaplan-Meier analysis of the time until the first use of each treatment (the "event") for all patients as a function of time was also performed
- A multivariable logistic regression model examined the presence of depression/anxiety in the patient cohort while controlling for patient characteristics including gender, age, and geographic region, any post-index hyperhidrosis treatment, and five common comorbidities (respiratory infections, other lower respiratory infections, other upper respiratory infections, other gastrointestinal disorders, and other skin conditions) identified by the AHRQ software[6] in this sample
- Comparisons between cohorts were performed with t-tests or chi-square statistics, as appropriate
- *P* values were computed with clustering to account for dependence between subjects due to matching; Z-tests using robust standard errors in an Ordinary Least Squares regression were used for continuous measures, and Rao-Scott tests were used for binary measures
- Depression and anxiety claims were summarized for the baseline period, the total follow-up period, and new claims made only during the follow-up period

RESULTS

Sample Selection

- Of 309,709 individuals identified with at least 1 claim for a prescription-strength antiperspirant or an ICD code for hyperhidrosis, 44,484 patients met selection criteria for inclusion in the hyperhidrosis cohort; the control cohort was comprised of 137,451 patients

Patient Characteristics

- Patients in the hyperhidrosis cohort were a mean age of 36.5 ± 16.5 years (CC=40.2 ± 16.9); 83.5% were ≥18 years of age (CC=87.8%), and 58.5% were female (CC=56.0%)
- The baseline comorbid conditions that showed the greatest difference in frequency between the hyperhidrosis and control cohorts were respiratory infections (39.0% hyperhidrosis vs. 30.7% control) and other skin disorders (30.9% hyperhidrosis vs 20.5% control) (**Table 1**)
  - Acne (9%), rash and other non-specific skin eruption (3%), and actinic keratosis (3%) were the most common comorbid skin disorders in the hyperhidrosis cohort (CC= 6%, 3%, and 3%, respectively)

Table 1. Common Patient Comorbidities at Baseline

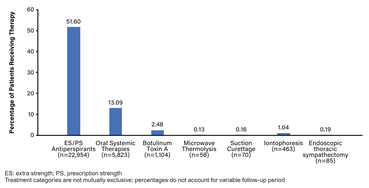
AHRQ comorbidities		Hyperhidrosis Cohort (N=44,484)	Control Cohort (N=137,451)
Respiratory infections	n	17,330	42,227
	%	38.96	30.72
Other skin disorders	n	13,734	28,187
	%	30.87	20.51
Other connective tissue disease	n	12,745	33,509
	%	28.65	24.38
Disorders of lipid metabolism	n	8,929	29,148
	%	20.07	21.21
Non-traumatic joint disorders	n	10,623	29,874
	%	23.88	21.73
Spondylosis; intervertebral disc disorders; other back problems	n	10,338	27,537
	%	23.24	20.03
Diseases of female genital organs	n	9,685	25,605
	%	21.77	18.63
Eye disorders	n	9,179	26,153
	%	20.63	19.03
Other lower respiratory disease	n	8,840	20,785
	%	19.87	15.12
Hypertension	n	8,220	27,769
	%	18.48	20.20

All comorbid conditions listed were significantly higher in the hyperhidrosis vs control cohort (*P*<0.001) except disorders of lipid metabolism and hypertension, which were significantly higher in the control cohort (*P*<0.001)
As sample sizes were large, statistical significance was easily achieved due to overpowering.
P values were computed with clustering; Rao-Scott test was used for binary measures
Comorbidities were identified by Clinical Classification Software for ICD-9-CM/ICD-10-CM codes from the AHRQ
AHRQ, Agency for Healthcare Research and Quality; ICD, International Classification of Disease

Treatment Patterns

- A slight majority of patients in the hyperhidrosis cohort (51.6%) received treatment with prescription antiperspirants, while 13.1% had prescription fills for oral systemic therapies; a very small percentage of the hyperhidrosis sample received procedures for hyperhidrosis treatment, including botulinum toxin A (**Figure 1**)
- Prescription antiperspirants were the earliest initiated therapies in the hyperhidrosis cohort during the variable follow-up period, with a mean ± SD time to first prescription fill of 1.4 ± 6.3 months (**Table 2**); this is consistent with the International Hyperhidrosis Society (IHhS) clinical treatment algorithm, which generally recommends antiperspirants as a first line of therapy for hyperhidrosis
  - While glycopyrronium cloth is also recommended by the IHhS as a first line treatment for primary axillary hyperhidrosis, the therapy was not available in the US until October 2018; since the study included data through November 2018, there were very few prescriptions made for glycopyrronium cloth (n=6) in this dataset, precluding meaningful analysis of the treatment option
- On average, other treatments were not initiated until over a year after the index date, including oral systemic therapies, which had a mean time to initiation of 16.9 ± 19.1 months (**Table 2**)
  - These results were confirmed with Kaplan-Meier analyses of adjusted time to treatments and procedures (**Figure 2**)
- The incidence rate shows the average frequency of treatment for patients in a given year; incidence rates adjusted for the variable follow-up period ranged from 0.29 (endoscopic thoracic sympathectomy) to 1.80 (oral systemic therapies) per person years (**Table 2**)
- Adherence to prescription medications was low over 12 months, with mean ± SD PDC of only 0.13 ± 0.09 for prescription antiperspirants and 0.30 ± 0.28 for oral systemic therapies (**Table 2**)

Figure 1. Treatments in the Hyperhidrosis Cohort



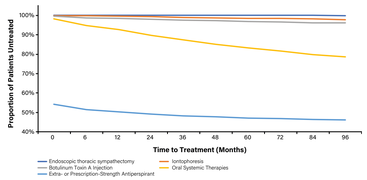
ES; extra strength; PS, prescription strength
Treatment categories are not mutually exclusive; percentages do not account for variable follow-up period

Table 2. Hyperhidrosis Cohort (n=44,484) Therapies and Procedures

Therapy or Procedure	Time to First Occurrence of Therapy /Procedure (Months), Mean (SD)[a]	Incidence Rates			Proportion of Days Covered (PDC)[b], Mean (SD)
		Events	Person Years	Rate per Person Years	
Prescription-Strength Antiperspirants (n=22,954)	1.4 (6.3)	57,756	83,472	0.69	0.13 (0.09)
Oral Systemic Therapies (n=5,823)	16.9 (19.1)	40,965	22,709	1.80	0.30 (0.28)
Botulinum Toxin A (n=1,104)	15.1 (19.5)	3,683	4,530	0.81	
Microwave Thermolysis (n=58)	19.9 (17.8)	379	239	1.59	
Suction Curettage (n=70)	19.7 (18.2)	105	279	0.38	
Iontophoresis (n=463)	22.9 (20.8)	1,733	2,097	0.83	
Endoscopic Thoracic Sympathectomy (n=85)	15.0 (21.8)	98	338	0.29	

[a]Times do not account for variable follow-up period within sample
[b]Proportion of days covered (PDC) was calculated for prescription medications and/or prescription-strength antiperspirants only

Figure 2. Kaplan-Meier Analysis of Adjusted Time to Treatments and Procedures

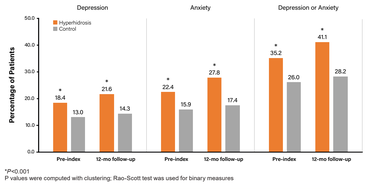


Glycopyrronium cloth, microwave thermolysis, and suction curettage were also measured; very few patients had these treatments and their trend lines are therefore not shown
Log-rank test was used for assessing equality of survival distributions

Emotional Health Characteristics

- The percentage of patients with depression or anxiety (**Figure 3**) during the 12-month baseline (pre-index) period was 35% in the hyperhidrosis cohort (CC=26%, *P*<0.001)
- This percentage increased during the 12-month follow-up period, with a significantly higher percentage of patients in the hyperhidrosis cohort with reports of depression or anxiety than in the control group (41.1% vs 28.2%, *P*<0.001), as well as with newly diagnosed depression or anxiety (18.2% vs 10.6%, *P*<0.001)
- Patients in the hyperhidrosis cohort had nearly 1.8 times higher odds of depression or anxiety than those in the control cohort while controlling for other variables (odds ratio=1.76, 95% confidence interval 1.7-1.8, *P*<0.001; **Table 3**)
- Older patients, females, and subjects with comorbid conditions, particularly gastrointestinal disorders, were more likely to experience depression or anxiety (**Table 3**)

Figure 3. Patients with Depression and/or Anxiety During Pre-Index and Follow-Up Periods



*P<0.001
P values were computed with clustering; Rao-Scott test was used for binary measures

Table 3. Logistic Regression Model of 12-month Post-Index Depression or Anxiety

Independent Variables	Post-Index Depression or Anxiety			
	Odds Ratio	Lower 95% CI	Upper 95% CI	*P* value
Hyperhidrosis cohort	1.756	1.715	1.798	<0.001
AHRQ Comorbidities				
Respiratory infections	1.278	1.249	1.308	<0.001
Other lower respiratory infections	1.434	1.395	1.475	<0.001
Other upper respiratory infections	1.242	1.207	1.279	<0.001
Other gastrointestinal disorders	1.824	1.767	1.882	<0.001
Other skin conditions	1.197	1.168	1.226	<0.001
Gender				
Female	1.751	1.714	1.789	<0.001
Male	ref.	–	–	–
Age				
<9	0.160	0.136	0.189	<0.001
9-17	0.368	0.355	0.382	<0.001
18-24	0.643	0.621	0.665	<0.001
25-34	0.781	0.758	0.804	<0.001
35+	ref.	–	–	–

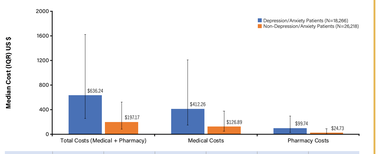
Observations read = 181,935, Observations used= 181,935
AHRQ, Agency for Healthcare Research and Quality; CI, confidence interval

Healthcare Costs and HCRU

- While the distribution pattern of costs within the hyperhidrosis cohort was similar between patients with depression/anxiety and those without, patients with depression/anxiety had significantly higher mean [median] all-cause total costs ($1905 [$636] vs $673 [$197]; *P*<0.001, and all-cause medical costs ($1598 [$412] vs $544 [$127]; *P*<0.001) than those without depression/anxiety (**Figure 4**A)
  - On average, ambulatory costs were the source of highest medical expense for patients both with and without depression/anxiety (**Figure 4**B)

Figure 4. Follow-up Health Care Costs within the Hyperhidrosis Cohort

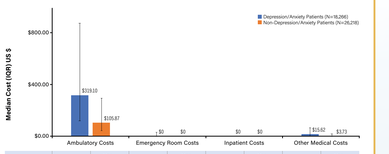
A. Overall Medical and Pharmacy Costs



	Depression/ Anxiety (N=18,266)	Non-Depression/ Anxiety (N=26,218)	Depression/ Anxiety (N=18,266)	Non-Depression/ Anxiety (N=26,218)	Depression/ Anxiety (N=18,266)	Non-Depression/ Anxiety (N=26,218)
Mean	$1,905.39	$672.91	$1,598.12	$543.92	$307.28	$128.99
SD	$5,050.82	$2,202.78	$4,865.60	$2,015.12	$739.93	$633.40

P<0.001 for all comparisons between patients with and without depression/anxiety based on mean values
IQR, interquartile range

B. Medical Costs by Encounter

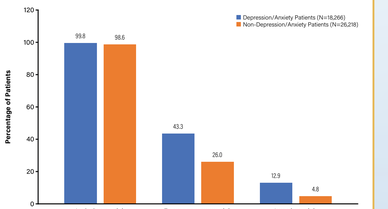


	Depression/ Anxiety (N=18,266)	Non-Depression/ Anxiety (N=26,218)	Depression/ Anxiety (N=18,266)	Non-Depression/ Anxiety (N=26,218)	Depression/ Anxiety (N=18,266)	Non-Depression/ Anxiety (N=26,218)	Depression/ Anxiety (N=18,266)	Non-Depression/ Anxiety (N=26,218)
Mean	$940.41	$360.40	$39.29	$13.26	$481.20	$122.69	$137.22	$47.58
SD	$2,411.34	$1,219.50	$222.33	$62.64	$3,057.61	$1,060.43	$789.99	$539.02

P<0.001 for all comparisons between patients with and without depression/anxiety based on mean values; IQR, interquartile range

- A significantly higher percentage of patients with depression/anxiety had an inpatient stay (12.9% vs 4.8%; *P*<0.001) and emergency room visit (43.3% vs 26.0%; *P*<0.001) when compared with patients who did not have depression/anxiety (**Figure 5**)

Figure 5. Follow-up Health Care Resource Utilization within the Hyperhidrosis Cohort



All patient comparisons were significant at *P*<0.001

Limitations

- Acknowledging that errors may occur with diagnosis codes and claims, the risk of misidentifying hyperhidrosis was mitigated by the requirement of at least two claims indicating the condition for patient study inclusion; identification of depression or anxiety required a single claim
- Codes for procedures and oral systemic therapies were generally not specific to the treatment of hyperhidrosis; this was addressed by excluding patients with non-specific codes for these procedures or pharmacy codes for oral systemic therapies within seven days before or after the index date
  - However, all instances of these procedures and medications (codes for botulinum toxin A, microwave thermolysis, suction curettage, iontophoresis, endoscopic thoracic sympathectomy, and pharmacy codes for oral systemic therapies) were counted in the follow-up period, which may have led to an overestimation of the frequency of the procedures used for hyperhidrosis treatment
- Results and conclusions are limited to patients enrolled in managed care plans accessible from the Optum Research Database and may not be generalizable to other commercially insured populations in the US
- Prescriptions filled outside the pharmacy benefit (out-of-pocket), drug samples, and over-the-counter medications were not captured, which could potentially overestimate the proportion of untreated patients; this is of particular note since over-the-counter antiperspirants may be appropriate for some hyperhidrosis patients
- Counts and percentages of treatments and procedures used, as well as mean time to first receipt of treatments do not account for censoring; incidence rates, along with Kaplan-Meier analyses of adjusted time to treatment were included to address the variable follow-up period
- The potential relationship between treatment of hyperhidrosis and a diagnosis of depression and/or anxiety was not assessed, and the observational study design precludes causal assessment of the relationship between hyperhidrosis and anxiety and/or depression
- There may be confounding variables other than the presence of anxiety and depression that could have driven the differences in HCRU and costs; multivariable regression analysis was not conducted, and the relationship between depression or anxiety and outcomes is further confounded because depression/anxiety cohort assignment was based on follow-up diagnoses

CONCLUSIONS

- This real-world observational data analysis shows that substantial comorbid depression and anxiety exist among patients in a hyperhidrosis cohort relative to a control group, both prior to and following diagnosis of hyperhidrosis or following a prescription for excessive sweating
  - Other comorbidities at baseline (eg, respiratory conditions and other skin conditions) were more common in the hyperhidrosis cohort, which may underlie some differential patterns of healthcare resource utilization relative to the control cohort
- Adherence (defined by proportion of days covered) to prescription antiperspirants and oral systemic therapies was poor, suggesting that tolerability and efficacy may be limiting factors to effective treatment of hyperhidrosis
- In patients with hyperhidrosis, all-cause health care costs and HCRU were significantly higher in those who experienced depression/anxiety when compared to those without depression/anxiety
- These results demonstrate higher overall health care burden for the hyperhidrosis patient population
- Further research and provider attention are needed to elucidate the emotional burden experienced by patients following a diagnosis of hyperhidrosis

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DISCLOSURES

SZK: employed by Dermira as a consultant; KKG: employee of Dermira, Inc., a wholly-owned subsidiary of Eli Lilly and Company; MH: employee of Optum at the time study was conducted, which received funding for this research; JPB: employee of Optum, which received funding for this research

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