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A Retrospective Comparative Analysis of Cutaneous Adverse Reactions in GLP-1 Agonist Therapies

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ABSTRACT

Glucagon-like peptide-1 (GLP-1) agonists are used to treat type 2 diabetes mellitus (T2DM) and have recently gained approval and popularity for treating obesity and weight loss. There is a lack of data evaluating the types of reactions associated with this medication class, and this study aimed to characterize the types of cutaneous reactions seen across different GLP-1 agonists, and whether differences exist in reactions based on the reason for medication use. Through a retrospective review of cutaneous adverse events associated with semaglutide, dulaglutide, tirzepatide, lixisenatide, liraglutide, and exenatide in the FDA Adverse Event Reporting System, it was found that the 5 most common cutaneous reactions associated with GLP-1 agonists were eczematous, pruritus, drug eruptions, hyperhidrosis, and alopecia. Life-threatening cutaneous adverse events accounted for 2.17% of all cutaneous reactions, with no statistically significant differences observed between drug types. It was also found that GLP-1 agonist use for T2DM exhibited significantly higher rates of alopecia (P=0.000) and hyperhidrosis (P=0.000) in comparison to use for weight management.

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INTRODUCTION

Glucagon-like peptide-1 (GLP-1) agonists are used to treat type 2 diabetes mellitus (T2DM) and have recently gained approval and popularity for treating obesity and weight loss. With the recent increase in prescriptions,[1] a notable gap in the literature still exists regarding comprehensive evaluations and comparisons of cutaneous reactions in this medication class. This study aimed to characterize the types of cutaneous reactions seen across different GLP-1 agonists and to determine whether differences exist in reactions based on the reason for medication use.

Cutaneous adverse events (CAEs) to GLP-1 agonists were retrospectively reviewed using the FDA Adverse Event Reporting System (FAERS).[2] Medications reviewed included: semaglutide, dulaglutide, tirzepatide, lixisenatide, liraglutide, and exenatide. Adverse events (AEs) reviewed were limited to those categorized as "Skin and Subcutaneous Tissue Disorders" reactions with a single suspected offending drug from the previously listed medications. Reactions were grouped into categories such as life-threatening, drug eruptions, eczematous reactions, etc, (Table 1). CAEs were then filtered and grouped into the reason for use in the following groups: T2DM, weight management (WM), and T2DM+WM. Chi-Square (or Fisher's

TABLE 1.

Reaction Groupings
Reactions
Life-threatening (includes Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms, Angioedema, and Pemphigus)
Drug eruptions (includes urticaria, erythema, erythema multiforme, erythema nodosum, pemphigoid, and fixed drug eruptions)
Eczematous (includes Rash, Dry Skin, and Dermatitis)
Alopecia
Hyperhidrosis
Pruritus
Acne
Photosensitivity Reactions
Discoloration
Purpura and Petechiae
Nail Changes
Psoriasis
Hidradenitis Suppurativa
Skin Laxity
Mucosal Blistering

Exact Test as appropriate) with Bonferonni adjusted *P*-values was utilized to determine the relative rates of reactions and to compare these rates amongst medications and reasons for use. This study utilized publicly available data and therefore was exempt from IRB approval.

CAEs accounted for approximately 5% (n=10,926) of the total reported AEs (n=220,872). 11,576 reactions were reported within the 10,926 CAEs (multiple reactions listed for some events). Of the total reported reactions, exenatide accounted for the largest proportion (42.4%, n=4,904) followed by dulaglutide (20.1%, n=2,331). The five most common reaction types were eczematous (27.0%, n=3,127), pruritus (22.3%, n=2,587), drug eruptions (19.1%, n=2,207), hyperhidrosis (15.2%, n=1,759), and alopecia (10.0%, n=1,162) (Table 2). Life-threatening CAEs accounted for 2.17% (n=251) of reactions, with no statistically significant differences observed between drug types (Table 2). Significant differences existed between drug types for eczematous reactions (*P*=0.000), pruritus (*P*<0.001), drug eruptions (*P*=0.000), hyperhidrosis (*P*=0.000), alopecia (*P*=0.000), discoloration (*P*=0.014), and acne (*P*=0.028) (Table 2). CAEs were then filtered by reason for use. 7,803 reactions were related to GLP-1 agonist use for T2DM (90.03%, n=7,025), WM (9.16%, n=715), and T2DM+WM (0.81%, n=63) (Table 3). Of note, alopecia (*P*=0.000) and hyperhidrosis (*P*=0.000) reactions were significantly more likely to be associated with use of T2DM in comparison to WM.

To our knowledge, there is limited data that quantifies and characterizes CAEs associated with GLP-1 agonist use. Our study found that patients may experience pruritus, eczematous reactions, drug eruptions, hyperhidrosis, and alopecia when taking GLP-1 agonists. Additionally, even though hair loss has been associated with rapid weight loss and nutritional deficiencies,[3,4] alopecia was more significantly associated with T2DM. As the prescriptions of GLP-1 agonists continue to increase, providers should be aware of associated CAEs and equipped to counsel and manage patients accordingly. More research is needed to determine whether CAEs from GLP-1 agonists are a significant concern.

TABLE 2.

Associated Reactions With GLP-1 Agonists Grouped by Medication

	Semaglutide	Dulaglutide	Tirzepatide	Liraglutide	Exenatide	Lixisenatide	Total reactions (n, % within total reactions)	*P*-value
Life-threatening	43	59	7	49	93	0	251 (2.17%)	0.083
Eczematous	533^{a,b}	769^{b}	183^{a,c}	580^{a,b}	1059^{c}	3^{a,b,c}	3127 (27.0%)	0.000*
Pruritus	401^{a,b}	515^{a,b}	130^{b}	409^{a,b}	1127^{a}	5^{c}	2587 (22.3%)	<0.001*
Drug eruptions	228^{a}	422^{b}	151^{b,c}	351^{b}	1052^{c}	3^{a,b,c}	2207 (19.1%)	0.000*
Hyperhidrosis	164^{a}	238^{a,b}	39^{c}	237^{b}	1081^{d}	0^{a,b,c,d}	1759 (15.2%)	0.000*
Alopecia	239^{a}	239^{b}	155^{c}	251^{a,b}	278^{d}	0^{a,b,c,d}	1162 (10.0%)	0.000*
Discoloration	28^{a,b}	30^{a,b}	8^{a,b}	21^{b}	103^{a}	0^{a,b}	190 (1.64%)	0.014*
Acne	12^{a}	20^{a}	5^{a}	21^{a}	27^{a}	1^{b}	86 (0.74%)	0.028*
Nail changes	10	8	3	13	37	0	71 (0.61%)	0.281
Psoriasis	9	15	4	15	18	0	61 (0.53%)	0.279
Photosensitivity reaction	6	8	4	6	16	0	40 (0.35%)	0.855
Purpura and Petechiae	3	5	0	2	8	0	18 (0.16%)	0.853
Hidradenitis Suppurativa	3	0	0	1	2	0	6 (0.05%)	0.206
Mucosal Blistering	1	2	0	1	2	0	6 (0.05%)	0.954
Skin laxity	1	1	1	1	1	0	5 (0.04%)	0.365
Total reactions associated with drug type (n, % within total reactions)	1681 (14.5%)	2331 (20.1%)	690 (5.96%)	1958 (16.9%)	4904 (42.4%)	12 (0.10%)	11576	--

**P*-value ≤ 0.05 was considered statistically significant. Differing lettered subscripts across reaction rows indicate statistical significance between drug types.

TABLE 3.

Associated Reactions With GLP-1 Agonists Grouped by Reason for Medication Use

	Type 2 Diabetes Mellitus	Weight Management	T2DM + Weight Management	Total reactions (n, % within total reactions)	*P*-value
Life-threatening	151	14	1	166 (2.13%)	0.901
Eczematous	1696	161	15	1872 (24.0%)	0.118
Pruritus	1604	156	13	1773 (22.7%)	0.159
Drug eruptions	1361	133	14	1508 (19.3%)	0.446
Hyperhidrosis	1373[a]	100[b]	9[a,b]	1482 (19.0%)	0.000*
Alopecia	542[a]	121[b]	10[a,b]	673 (8.62%)	0.000*
Discoloration	123	10	0	133 (1.70%)	0.476
Acne	44	10	0	54 (0.69%)	0.100
Nail changes	47	6	1	54 (0.69%)	0.444
Psoriasis	36	3	0	39 (0.50%)	1.000
Photosensitivity reaction	23	1	0	24 (0.31%)	0.782
Purpura and Petechiae	14	0	0	14 (0.18%)	0.468
Hidradenitis Suppurativa	3	0	0	3 (0.04%)	1.000
Mucosal Blistering	4	0	0	4 (0.05%)	1.000
Skin laxity	4	0	0	4 (0.05%)	1.000
Total reactions associated with the reason for use (n, % within total reactions)	7025 (90.03%)	715 (9.16%)	63 (0.81%)	7803	--

*P-value ≤ 0.05 was considered statistically significant. Differing lettered subscripts across reaction rows indicate statistical significance between reason for use.

DISCLOSURES

The authors have no conflict of interest to disclose.

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