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Risk Factors Associated With Treatment Discontinuation and Down-titration in Type 2 Diabetes Patients Treated With Sulfonylureas

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Introduction

- Diabetes mellitus is a chronic, progressive disease affecting approximately 24.4 million adults in the United States.
- Type 2 diabetes mellitus (T2DM) accounts for 85% to 95% of all diabetes cases.
- Sulfonylureas (SU) represent one class of oral antihyperglycemic agents (OAHA) introduced into clinical practice in the 1950s as a treatment for T2DM.
- Although effective, SUs present the risk of prolonged hypoglycemia, weight gain, and possibly cardiovascular events.

Objectives

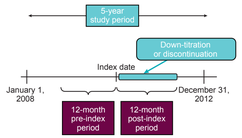
- To describe the rate of discontinuation and down-titration in patients with T2DM treated with SUs
- To assess time to therapy changes (discontinuation or down-titration) for patients treated with SUs
- To identify risk factors associated with discontinuation or down-titration for patients treated with SUs

Methods

Study Design and Patient Selection

- A retrospective cohort study using the Truven Health MarketScan® Databases.
  - MarketScan is a large insurance claims database that includes patient-level medical and pharmacy claims histories of 180 million covered lives enrolling in 25 national and regional health plans in the US.
  - The database is representative of the national commercially insured population and those who have both Medicare coverage and supplemental employer-sponsored coverage. It captures the full continuum of care in multiple settings, including physician office visits, hospital stays, and outpatient pharmacy claims.
- This analysis includes data from the Commercial Claims and Encounters and the Medicare Supplemental and Coordination of Benefits databases between January 1, 2008, and December 31, 2012 (study period).

Figure 1. Study Design



Inclusion Criteria

- Patients with at least one prescription of an SU in the study period, with the index date being the date of the 1st SU prescription.
- Patients aged at least 18 years or older as of the index date.
- At least one year pre- and post-index continuous enrollment in the MarketScan database.

Exclusion Criteria

- Patients with type 1 diabetes (ICD-9 code: 250.x1 and 250.x3) during the study period.
- Patients with gestational diabetes (ICD-9 code: 648.8) during the study period.
- Patients with any secondary diabetes (ICD-9 code: 249.x) during the study period.
- Patients with insulin prescriptions (ICD-9 code: V58.67) within 1 year before the index date.

Assessment of Discontinuation and Down-titration

- Patients were classified into one of the three mutually exclusive groups based on therapy change:
  - Discontinuation (discontinuers): When the subsequent dispense date was ≥90 days apart from the end date of the preceding SU dispense. The discontinuation date is defined as the end date of the preceding SU dispense.
  - Down-titration (down-titraters): SUs were prescribed with a lower dose than the index dose. The date of the down-titration was the prescription date of the first SU with lower dose. Dose equivalence was considered when different SUs were prescribed to the patient during the follow-up period.
  - Continuation without down-titration (continuers): Patient continuously used the index drug with the same or higher equivalent dose for at least 12 months.

Statistical Analysis

- Descriptive analyses were conducted to examine the baseline patient characteristics.
- Between-group comparisons were assessed using Kruskal-Wallis nonparametric test for continuous variables and the chi-square test for categorical variables
- Kaplan-Meier (KM) method was used to estimate the distribution function for time-to-first-therapy change, defined as experiencing discontinuation or down-titration.
- Cox's proportional hazards regression was performed to evaluate the association between patient characteristics and treatment discontinuation in terms of hazard ratios (HRs) with down-titraters excluded.
- The same approach was used to evaluate the association between patient characteristics and down-titration by excluding discontinuers.
- In both regression models, post-index hypoglycemia was included as a time-varying independent variable.

Results

Table 1a. . Baseline Characteristics for Patients With T2DM Who Newly Initiated SU Therapy – Demographic Characteristics and Health Plan

	Overall (N=104,082)	Discontinuers (n=49,158; 47.2%)	Down-titraters (n=6,075; 5.8%)	Continuers (n=48,849; 46.9%)	*P*-Value
Male	56.2%	54.2%	57.1%	58.2%	<.0001
Age in years (mean [SD])	57.0 (12.3)	55.6 (12.7)	52.6 (12.5)	58.3 (11.7)	<.0001
Age group					<.0001
18-25	0.3%	0.5%	0.3%	0.1%	
26-35	3.3%	4.6%	3.1%	2.0%	
36-45	13.1%	15.8%	12.3%	10.3%	
46-55	29.0%	29.7%	29.0%	28.4%	
56-65	33.7%	30.9%	32.6%	36.7%	
66-75	12.0%	10.8%	12.5%	13.3%	
75 and above	8.6%	7.8%	10.2%	9.2%	
Region					<.0001
North central	28.3%	26.6%	29.1%	29.9%	
Northeast	9.0%	8.6%	8.5%	9.4%	
South	42.4%	45.3%	43.2%	39.4%	
West	17.1%	17.3%	16.1%	17.0%	
Unknown	3.2%	2.1%	3.2%	4.2%	
Health plan					<.0001
HMO	16.6%	17.3%	14.9%	16.1%	
POS	7.9%	8.1%	7.7%	7.8%	
PPO	53.2%	53.4%	54.7%	52.8%	
Other	22.3%	21.3%	22.7%	23.2%	

Table 1b. Baseline Characteristics for Patients With T2DM Who Newly Initiated SU Therapy – Comorbid Conditions and Generation of Index SU

	Overall (N=104,082)	Discontinuers (n=49,158; 47.2%)	Down-titraters (n=6,075; 5.8%)	Continuers (n=48,849; 46.9%)	*P*-Value
Microvascular complications					
Retinopathy/blindness	4.4%	3.9%	4.8%	4.8%	<.0001
Neuropathy	6.8%	6.8%	7.7%	6.7%	0.0135
Nephropathy	4.9%	4.6%	6.1%	5.1%	<.0001
Macrovascular complications					
Stroke	1.5%	1.5%	2.2%	1.4%	<.0001
Transient ischemic attack	1.2%	1.2%	1.6%	1.1%	0.0022
Congestive heart failure	4.3%	4.2%	5.2%	4.2%	0.0031
Myocardial infarction	2.1%	2.2%	2.7%	1.9%	0.0003
Ischemic heart disease, including angina	13.0%	12.4%	13.7%	13.4%	<.0001
Peripheral arterial diseases	4.4%	4.3%	5.3%	4.3%	
Hypertensive chronic kidney diseases	5.1%	5.2%	5.8%	5.0%	
Liver diseases	3.0%	3.3%	3.0%	2.7%	<.0001
Hypoglycemia	2.4%	2.6%	2.7%	2.2%	<.0001
Generation of index SU					<.0001
First generation	0.1%	0.0%	0.1%	0.1%	
Second generation	64.7%	65.2%	66.2%	63.9%	
Third generation	35.3%	34.7%	33.7%	36.1%	

Table 2. Time to First Therapy Change (Days)

	N	Mean (SD)	Median (IQR)
Any treatment change	55,233	124.2 (97.5)	91.0 (156)
Discontinue	49,158 (89%)	122.7 (97.2)	91.0 (154)
Down-titrate	6,075 (11%)	137.0 (99.1)	114.0 (150)

Table 3. Cox Proportional Hazards Regression Results for Time to Discontinuation

Variables	Hazard ratios	95% CI	P-value
Presence of post-SU hypoglycemia before discontinuation	1.78	(1.677, 1.894)	<.0001
Male	0.90	(0.880, 0.912)	<.0001
Health plan type			
POS vs. HMO	1.00	(0.962, 1.040)	
PPO vs. HMO	1.03	(0.999, 1.052)	
Other vs. HMO	1.02	(0.990, 1.054)	
Index age group			<.0001
26-35 vs. 18-25	0.77	(0.683, 0.882)	
36-45 vs. 18-25	0.61	(0.540, 0.690)	
46-55 vs. 18-25	0.47	(0.419, 0.535)	
56-65 vs. 18-25	0.40	(0.359, 0.458)	
66-75 vs. 18-25	0.38	(0.338, 0.433)	
75 or older vs. 18-25	0.37	(0.328, 0.422)	
Region			<.0001
North central vs. west	0.95	(0.924, 0.980)	
Northeast vs. west	0.98	(0.941, 1.016)	
South vs. west	1.10	(1.074, 1.133)	
Unknown vs. west	0.60	(0.566, 0.645)	
Generation of the index SU			0.0026
First vs. third generation	0.94	(0.603, 1.372)	
Second vs. third generation	1.03	(1.014, 1.053)	
Uses of combination therapy			
Metformin	0.82	(0.801, 0.831)	<.0001
Thiazolidinedione	0.94	(0.915, 0.969)	<.0001
Insulin	1.48	(1.401, 1.565)	<.0001
Meglitinides	0.99	(0.882, 1.104)	
GLP-1 agonists	0.92	(0.858, 0.987)	0.0208
DPP-4 inhibitors	0.88	(0.857, 0.911)	<.0001
Alpha-glucosidase inhibitors	1.07	(0.838, 1.341)	
Amylin analog	1.03	(0.256, 2.672)	
Other antidiabetic agents	1.20	(0.780, 1.746)	
Baseline comorbidities			
Microvascular complications			
Retinopathy/blindness	0.92	(0.874, 0.958)	0.0002
Neuropathy	1.04	(1.000, 1.074)	0.0487
Nephropathy	0.92	(0.876, 0.956)	<.0001
Macrovascular complications			
Stroke	1.07	(0.986, 1.154)	
Transient ischemic attack	1.03	(0.945, 1.126)	
Congestive heart failure	1.03	(0.982, 1.078)	
Myocardial infarction	1.11	(1.035, 1.179)	0.0024
Ischemic heart disease, including angina	1.01	(0.983, 1.045)	
Peripheral arterial diseases	1.09	(1.038, 1.136)	0.0003
Hypertensive chronic kidney diseases	1.07	(1.027, 1.118)	0.0014
Liver diseases	1.09	(1.036, 1.145)	0.0007
Hypoglycemia	0.97	(0.910, 1.024)	

Insignificant P-values were omitted for clean presentation.

Figure 2. Kaplan-Meier Curve for Time to First Therapy Change (Discontinuation or Down-titration)

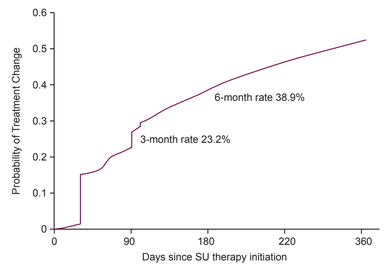


Table 4. Cox Proportional Hazards Regression Results for Time to Down-titration

Variables	Hazard ratios	95% CI	*P*-value
Presence of post-SU hypoglycemia before down-titration	2.79	(2.398, 3.231)	<.0001
Health plan type			0.0025
POS vs. HMO	1.10	(0.978, 1.233)	
PPO vs. HMO	1.16	(1.071, 1.254)	
Other vs. HMO	1.09	(0.995, 1.199)	
Index age group			<.0001
26-35 vs. 18-25	0.78	(0.487, 1.324)	
36-45 vs. 18-25	0.60	(0.381, 1.003)	
46-55 vs. 18-25	0.51	(0.330, 0.863)	
56-65 vs. 18-25	0.45	(0.290, 0.759)	
66-75 vs. 18-25	0.48	(0.304, 0.802)	
75 or older vs. 18-25	0.54	(0.342, 0.909)	
Region			<.0001
North central vs. West	1.06	(0.978, 1.156)	
Northeast vs. West	0.99	(0.885, 1.105)	
South vs. West	1.19	(1.095, 1.282)	
Unknown vs. West	0.79	(0.674, 0.929)	
Generation of the index SU			0.0001
First vs. third generation	1.95	(0.773, 3.963)	
Second vs. third generation	1.12	(1.057, 1.178)	
Uses of combination therapy			
Thiazolidinedione	1.09	(1.009, 1.174)	0.0272
Insulin	1.82	(1.563, 2.113)	<.0001
Amylin analog	5.95	(1.473, 15.484)	0.0021
Baseline comorbidities			
Neuropathy/Neuropathy	1.12	(1.020, 1.235)	0.0166
Nephropathy	1.16	(1.036, 1.292)	0.0087
Stroke	1.37	(1.129, 1.642)	0.0010
Myocardial infarction	1.30	(1.097, 1.536)	0.0021
Peripheral arterial diseases	1.14	(1.010, 1.279)	0.0318

Same covariates were applied. Results with insignificant P-values were omitted due to limited space.

Summary

- Within one year following SU initiation, 47.2% of patients discontinued SU therapy, and 5.7% of patients had SU dose down-titration.
- The rates of treatment changes at 3 and 6 months were 23.2% and 38.9%, respectively.
- Among those with treatment changes, average time to first therapy change was approximately 124 days (123 days for discontinuation and 137 days for down-titration).
- Post-index hypoglycemia was associated with both discontinuation and down-titration.
- The effects of post-index hypoglycemia on SU discontinuation and SU down-titration differed in magnitude. Patients with post-index hypoglycemia were much more likely to be down-titrated than discontinued, as the post-index hypoglycemia was associated with 179% increase in the rate of down-titration (HR=2.79) and 78% increase in the rate of discontinuation (HR= 1.78).
- Rate of SU discontinuation was lowest among those 66 and older, with an overall decreasing rate of discontinuation with respect to age, while the rate of SU down-titration was lowest among those 56 to 75 years.
- Concomitant use of insulin was associated with a 48% increase in the rate of SU discontinuation and an 82% increase in the rate of SU dose down-titration.
- In general, baseline comorbidities were associated with SU discontinuation and SU down-titration.

Limitations

- The MarketScan databases are representative of the national commercially insured population and those who have both Medicare and supplemental coverage. Therefore, our findings might not be generalizable to those covered by Medicare only, Medicaid, or those who are uninsured.
- Laboratory measures (i.e. HbA_{1c}) were not available for all patients in the database.
- Therapy change was determined based on dispense data. It is unknown whether the medication was actually taken by the patient or taken as prescribed.
- Types of therapy change were determined based on the first change. Subsequent therapy changes (i.e. down-titration followed by discontinuation) were not considered.
- Other unobserved confounding factors that were not available in the data could impact the study results.

Conclusions

- More than half of T2DM patients who newly initiated SU therapy experienced discontinuation or dose down-titration within 1 year following SU initiation.
- Insulin use and hypoglycemic events increased the risk of SU therapy changes.

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