Medication Adherence and Direct Medical and Prescription Cost Impact of Fixed-Dose vs Loose-Dose Thiazolidinedione Combination Products among Type 2 Diabetes Mellitus Patients

Brook RA,[1] Kleinman NL,[2] Wingenbach D,[3] Bron MS,[4] Baran RW[5]

[1]Head, Retrospective Analysis, JeSTARx Group, Newfoundland, NJ; [2]Director, Research Services, HCMS Group, Paso Robles, CA; [3]Research Analyst, HCMS Group, Cheyenne, WY; [4]Senior Principal Scientist, Health Economics & Outcomes Research, Takeda Global Research & Development Center, Inc., Deerfield, IL; [5]Senior Manager, Health Economics & Outcomes Research, Takeda Global Research & Development Center, Inc., Deerfield, IL

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BACKGROUND

The prevalence of diagnosed diabetes mellitus is 7% in the US population (all ages).[1] Type 2 diabetes mellitus (T2DM) accounts for 90% to 95% of all diagnosed cases of diabetes.[1]

Persistence with prescription (Rx) therapy is often suboptimal among patients with T2DM, resulting in impaired glycemic control, poor health outcomes, and increased resource utilization. Many patients with T2DM who are managed with oral anti-diabetic drugs (OADs) require polytherapy that may include combinations of:

- A thiazolidinedione (TZD), such as pioglitazone HCl or rosiglitazone maleate.
- Metformin, a biguanide.
- Sulfonylureas, which include products such as glyburide or glipizide.

Poor compliance and persistence with OADs have been documented, and when multiple OADs are needed to maintain glycemic control, nonpersistence may be exacerbated.

The OAD market now includes TZD combination products for pioglitazone (pioglitazone+metformin and pioglitazone+glimepiride) and rosiglitazone (rosiglitazone+metformin and rosiglitazone+glimepiride).

- It is important to understand the impact that FDC therapies have on compliance and cost.

OBJECTIVE

The goals of the current study were to assess the impact of fixed-dose (FDC) and loose-dose (LDC) combination thiazolidinedione (TZD) products on:

- Medication persistence.
- Point-of-service costs, which include medical and pharmacy costs.

METHODS

- A retrospective analysis was performed on data (2001 to 2006) from the Human Capital Management Services (HCMS) Research Reference Database consisting of approximately 510,000 employees representing the retail, service, manufacturing, and financial industries.
- Patients with T2DM were identified based on the presence of *International Classification of Diseases*, 9th Revision (ICD-9) diagnostic codes of 250.X0 (type 2 diabetes, not stated as uncontrolled) or 250.X2 (type 2 diabetes, uncontrolled).
- Patients with an Rx claim for metformin or a sulfonylurea, concurrent with a TZD (LDC) or combined with a TZD (FDC), were matched on demographics, job information, geography, and copayment in a 1:1 ratio.
- Index Date was assigned by the first FDC TZD Rx or the first occurrence of TZD within 45 days of metformin or sulfonylurea in the LDC component.
  - Index Dates before 31 May 2004 were required to avoid the FDC rosiglitazone plus metformin supply shortage between June 2005 and July 2006.
- Employees included in the analysis were required to be continuously employed and eligible for health benefits for at least 12 months after their Index Date.
- Because of the 12-month eligibility requirement and the timeframe of the study, the FDC cohort is represented by rosiglitazone plus metformin only, as it was the FDC with sufficient data during the study period.
- It is assumed that the FDC cohort is representative of the TZD class and pioglitazone+metformin specifically.
- Comparisons were made between 2 groups (FDCs and LDCs).
- Persistence was defined as the length of time the patient had a supply of both the TZD and either metformin or a sulfonylurea without a gap in supply of more than 30 days.
- Employee outcomes for both groups were compared over the 12 months following the Index Date and included:
  - Medication persistence decay curves.
  - Number of months of therapy was defined as the months of supply purchased during the 12 months following the Index Date.
  - Point-of-service direct costs.
    - Direct medical costs: doctor's office; inpatient hospital; outpatient hospital or clinic; emergency department; laboratory; pharmacy; and "other."

Statistical Analysis

- Employees in the LDC and FDC cohorts were matched 1:1 using logistic regression and propensity scores for age, tenure (years with current employer), sex, marital status, race, exempt/non-exempt status (exempt employees are not paid on an hourly basis and are not paid for overtime work), full-time/part-time status, salary, region (defined by first digit of employee's postal zip code), employer, and average copay.
- Comparisons between groups were made using Wilcoxon rank tests for persistence curves and chi-square (χ^2) tests for months-supply distributions and percent of employees reaching 90 days without a gap in supply.
- Two-part regression analysis was used to model the cost differences between the FDC and LDC cohorts using separate regression models for each component.
  - The models controlled for population differences in age, tenure (years with current employer), sex, marital status, race, exempt/non-exempt status (exempt employees are not paid on an hourly basis and are not paid for overtime work), full-time/part-time status, salary, Charlson Comorbidity Index,[2] and geography (defined by the first digit of the employee's postal zip code).
  - Differences were considered significant if P<0.05.

RESULTS

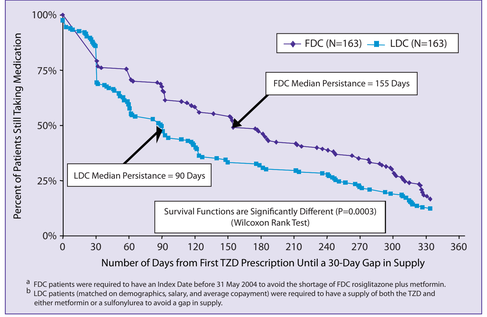
- Data were available for 163 matched subjects per cohort with no significant baseline differences (Table 1).
  - All subjects in the FDC cohort used rosiglitazone as TZD component.
  - Among the LDC cohort, 54% used pioglitazone and 49% used rosiglitazone.
- Following propensity-score matching, both cohorts averaged 41 years of age, were predominantly male (74% for FDC and 69% for LDC), were predominantly married (>66%), and worked full-time (>98%). The majority of employees in both cohorts were White (>50%).

Table 1. Descriptive Statistics

Variable	Diabetes Treated with TZD FDC Cohort (N=163) Mean (SE) or Percent (%)	Diabetes Treated with TZD LDC Cohort (N=163) Mean (SE) or Percent (%)
Age (years at Index Date)	46.00 (0.66)	47.57 (0.74)
Tenure (years at Index Date)	9.63 (0.69)	10.54 (0.81)
Annual salary (2007 US dollars)	49,228 (2,291)	47,060 (2,002)
Charlson Comorbidity Index Score	1.45 (0.09)	1.58 (0.10)
Female	26.4%	30.7%
Married	66.4%	71.6%
White	52.1%	54.6%
Black	19.2%	19.1%
Hispanic	23.3%	19.9%
Exempt	22.7%	20.2%
Full-time	98.8%	98.8%
Geography, 1st digit zip code		
0	5.5%	6.7%
1	3.1%	4.3%
2	9.2%	9.8%
3	20.2%	15.3%
4	2.5%	3.7%
5	1.2%	0.0%
6	4.3%	1.8%
7	42.9%	49.1%
8	4.9%	4.3%
9	6.1%	4.9%

- Persistence curves were significantly better for FDC (P=0.0003, Figure 1), with median persistence days of 155 for FDC compared with 90 days for LDC.
  - 67% of FDC patients reached 90 days persistence before having a 30-day gap in supply compared with 50% of LDC patients (P=0.0007).
  - Within the LDC cohort, the medication persistence curves were similar between the pioglitazone and rosiglitazone subcohorts.

Figure 1. Medication Persistence Curves: FDC[a] vs Matched LDC[b]



[a] FDC patients were required to have an Index Date before 31 May 2004 to avoid the shortage of FDC rosiglitazone plus metformin.
[b] LDC patients (matched on demographics, salary, and average copayment) were required to have a supply of both the TZD and either metformin or a sulfonylurea to avoid a gap in supply.

- All point-of-service costs (Table 2) were similar between the cohorts.
  - Overall costs as well as the individual direct medical costs and Rx costs all trended lower for the FDC cohort.

Table 2. Annual Point-of-Service Costs per Employee

Cost Category	Diabetes Treated with TZD FDC Cohort (N=163) Adjusted Mean Cost	Diabetes Treated with TZD LDC Cohort (N=163) Adjusted Mean Cost	Difference in Means
Doctor's office	$927	$1,226	-$299
Inpatient hospital	$495	$648	-$153
Outpatient hospital or clinic	$502	$583	-$80
Emergency department	$44	$72	-$28
Laboratory	$5	$9	-$4
Other	$16	$26	-$10
Prescription drug	$2,370	$2,678	-$308
Total direct health benefits	$4,361	$5,243	-$882
Total (minus Rxs)	$1,991	$2,564	-$574

All comparisons nonsignificant (P>0.05).
Costs are in 2007 US dollars.

Limitations

- Data availability at this time limits the composition of the FDC cohort.
- The composition of the FDC cohort serves as a surrogate for pioglitazone+metformin.

SUMMARY AND CONCLUSIONS

- Adherence as measured by persistency with FDC combination therapy was significantly better than with LDC.
- FDC TZD therapies provide an advantage for patients with T2DM.
- T2DM is associated with substantial direct cost (burden) of illness, which can be a large financial liability to employers.
- Management of T2DM with TZD combination therapies that foster compliance may reduce overall costs.
- These results indicate an opportunity for improved management of patients with T2DM, which may result in reduced costs from an employer perspective.
- This study suggests that:
  - Patients achieve compliance benefits from reduced medication burden by using FDC.
  - Additional research is needed with newer data in these cohorts to further inform us on long-term impact on compliance and cost.

REFERENCES

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