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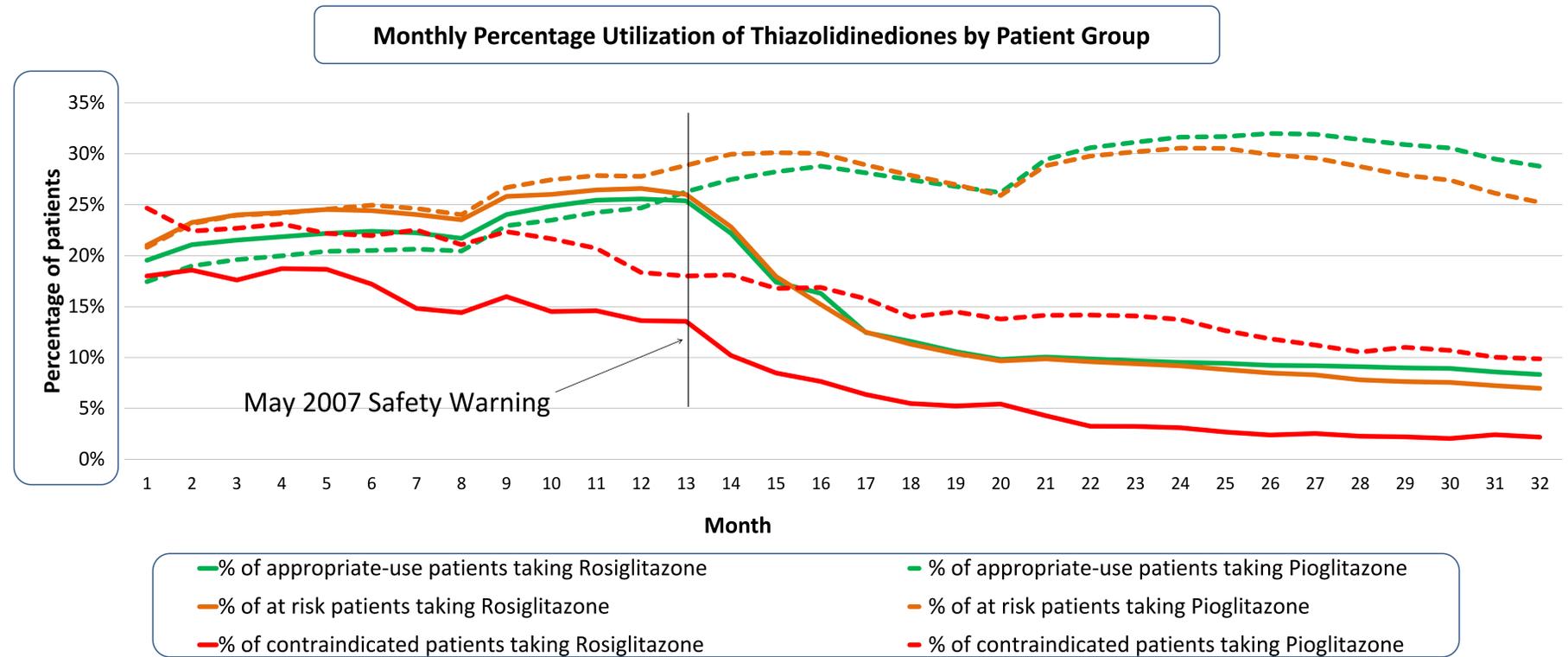
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BACKGROUND & OBJECTIVE

Poor adherence to Food and Drug Administration (FDA) safety alerts and warnings has the potential to expose patients to harmful effects of drugs. There is conflicting evidence on the adequacy of safety warnings to limit drug utilization in patients contraindicated to using thiazolidinediones (TZDs) (Wilkinson et al. 2004; Shah et al. 2010). Appropriate risk management should result in decreased use of a product in contraindicated patients while retaining use in appropriate patients. The objective of this study was to evaluate the impact of FDA safety warning about the cardiovascular safety of rosiglitazone on the utilization rates of thiazolidinedione oral anti-diabetes medications among indicated and non-indicated patients.

METHODOLOGY

A retrospective analysis of the five percent national sample of Medicare Part D beneficiaries for years 2006-2008 was conducted using an interrupted time series consisting of a 13-month pre-intervention period and a 19-month post-intervention period. Beneficiaries with at least one prescription claim for a TZD anti-diabetic during the study period were included in the sample. Beneficiaries were classified each month as non-user or rosiglitazone/pioglitazone user based on TZD possession. Beneficiaries were further classified each month during the study period into appropriate-use, at risk, and contraindicated groups based on the presence of certain comorbid conditions using ICD-9-CM diagnoses codes. Rosiglitazone and pioglitazone utilization rates were calculated each month for the beneficiaries in each appropriateness of use patient group. Segmented regression analysis was used to examine the effects of the May 2007 FDA safety warnings about the ongoing review of rosiglitazone's potential to increase cardiovascular risks on TZD utilization rates for the different appropriateness of use patient groups.



RESULTS

A graph showing the trend in TZD utilization rates by patient groups is presented. The full segmented regression model provides estimates of utilization level and trend before and after the FDA safety warning for each patient group. The full and most parsimonious segmented regression models reported below were used to estimate the relative difference in utilization rates for each patient group. There was an increasing trend in the total utilization rates of thiazolidinediones before the safety warning. Significant decline in drug utilization rates were observed at the end of the study period for all patient groups on rosiglitazone (relative difference -74.78%, -79.93%, and -90.21% in appropriate-use, at risk and contraindicated patient groups, respectively). The intervention did not have significant immediate effects on the post-intervention utilization rates of pioglitazone. However, after the intervention, a general decline in utilization of thiazolidinediones, including pioglitazone, was observed.

Full and Most parsimonious segmented regression models predicting the monthly utilization rate of rosiglitazone and pioglitazone in appropriate-use patients.

| Variable | Rosiglitazone | | | | Pioglitazone | | | |
|--|---------------|----------------|-------------|----------|--------------|----------------|-------------|----------|
| | Estimate | Standard Error | t-statistic | P-value | Estimate | Standard Error | t-statistic | P-value |
| a. Full segmented regression model | | | | | | | | |
| Intercept | 20.562 | 2.540 | 8.09 | < 0.0001 | 16.455 | 1.433 | 11.48 | < 0.0001 |
| Time | 0.117 | 0.280 | 0.42 | 0.6792* | 0.744 | 0.161 | 4.61 | < 0.0001 |
| Intervention | -2.445 | 1.100 | -2.22 | 0.0356 | 1.247 | 1.148 | 1.09 | 0.2869* |
| Time after intervention | -0.874 | 0.408 | -2.14 | 0.0421 | -0.561 | 0.220 | -2.56 | < 0.0001 |
| b. Most parsimonious segmented regression model | | | | | | | | |
| Intercept | 21.506 | 1.173 | 18.33 | < 0.0001 | 16.286 | 1.539 | 10.59 | < 0.0001 |
| Time | | | | | 0.805 | 0.163 | 4.93 | < 0.0001 |
| Intervention | -2.421 | 1.078 | -2.25 | 0.0333 | | | | |
| Time after intervention | -0.719 | 0.144 | -5.01 | < 0.0001 | -0.583 | 0.236 | -2.47 | 0.0198 |

Full and Most parsimonious segmented regression models predicting the monthly utilization rate of rosiglitazone and pioglitazone in at risk patients.

| Variable | Rosiglitazone | | | | Pioglitazone | | | |
|--|---------------|----------------|-------------|----------|--------------|----------------|-------------|---------|
| | Estimate | Standard Error | t-statistic | P-value | Estimate | Standard Error | t-statistic | P-value |
| a. Full segmented regression model | | | | | | | | |
| Intercept | 19.946 | 4.120 | 4.84 | < 0.0001 | 20.850 | 1.490 | 13.99 | < 0.001 |
| Time | 0.204 | 0.439 | 0.47 | 0.646* | 0.642 | 0.165 | 3.90 | < 0.001 |
| Intervention | 0.398 | 0.998 | 0.40 | 0.693* | 1.287 | 1.103 | 1.17 | 0.2534* |
| Time after intervention | -1.200 | 0.653 | -1.86 | 0.078 | -0.845 | 0.288 | -3.71 | < 0.001 |
| b. Most parsimonious segmented regression model | | | | | | | | |
| Intercept | 21.607 | 2.053 | 10.53 | < 0.0001 | 20.707 | 1.499 | 13.81 | < 0.001 |
| Time | | | | | 0.699 | 0.159 | 4.40 | < 0.001 |
| Intervention | | | | | | | | |
| Time after intervention | -0.909 | 0.209 | -4.53 | < 0.0001 | -0.853 | 0.230 | -3.72 | < 0.001 |

Full and Most parsimonious segmented regression models predicting the monthly utilization rate of rosiglitazone and pioglitazone in contraindicated patients.

| Variable | Rosiglitazone | | | | Pioglitazone | | | |
|--|---------------|----------------|-------------|----------|--------------|----------------|-------------|----------|
| | Estimate | Standard Error | t-statistic | P-value | Estimate | Standard Error | t-statistic | P-value |
| a. Full segmented regression model | | | | | | | | |
| Intercept | 19.428 | 1.017 | 19.11 | < 0.0001 | 24.790 | 0.670 | 36.99 | < 0.001 |
| Time | -0.485 | 0.119 | -4.09 | < 0.0001 | -0.450 | 0.828 | -5.43 | < 0.001 |
| Intervention | -4.618 | 0.953 | -4.84 | < 0.0001 | -1.222 | 0.766 | -1.60 | 0.1222* |
| Time after intervention | 0.073 | 0.115 | 0.47 | 0.6419* | 0.025 | 0.099 | 0.25 | 0.8030* |
| b. Most parsimonious segmented regression model | | | | | | | | |
| Intercept | 19.081 | 0.744 | 25.64 | < 0.0001 | 24.856 | 0.554 | 44.84 | < 0.001 |
| Time | | | | | -0.437 | 0.055 | -7.94 | < 0.0001 |
| Intervention | | | | | -4.598 | 0.941 | -4.88 | < 0.0001 |

* Significant variables dropped by stepwise elimination resulting in absence in the most parsimonious models

CONCLUSIONS

The initial warning about rosiglitazone's cardiovascular safety was effective in decreasing rosiglitazone's utilization in the targeted population and thus appeared to achieve the desired safety effects. However, the safety warning also had spillover effects by reducing utilization in non-targeted patient groups and of pioglitazone in the targeted population. This analysis demonstrates the importance of companies managing emerging risk issues in order to create market differentiation in use among different patient populations. This tactic, of appropriately differentiating patient populations, should be considered core to the ultimate strategic goals of marketing and risk management strategies when safety issues emerge later in product life cycles.

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