



Impact of Schedule IV controlled substance classification on carisoprodol utilization in the United States: An interrupted time series analysis

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ABSTRACT

Background: In January 2012, the Drug Enforcement Agency (DEA) classified carisoprodol as a Schedule IV controlled substance at the US federal level. We aimed to examine the effect of this policy on the use of carisoprodol in a commercially-insured population.

Methods: This interrupted time series study included individuals with musculoskeletal disorders in the IBM MarketScan Commercial Database between December 2009 and February 2014. We used comparative segmented linear regression to assess changes in the proportions of patients who filled/newly filled carisoprodol each month.

Results: A total of 13.3 million patients were included. 29 states with no scheduling prior to the DEA classification had lower baseline prevalence of carisoprodol use compared to 17 states that had scheduled carisoprodol individually before 2010 (11.0 vs. 21.1 patients with fills per 1000 patients). The federal scheduling was associated with an immediate decline (−1.12 per 1000 patients, $p < 0.01$) and decreasing trend in prevalence (−0.07 per 1000 patients per month, $p = 0.02$). This effect was not modified by existing state-level scheduling status. During the first, second, third, and fourth 6-month periods after federal scheduling, the relative difference between observed and predicted prevalence was 7.8%, 10.5%, 13.4%, and 19.8%. Similar patterns were observed for carisoprodol initiation. Overall, declining use was more pronounced among younger age groups and patients with injury.

Conclusions: Schedule IV controlled substance classification at the federal level was associated with a moderate reduction in the dispensing of carisoprodol regardless of whether scheduling was already present at the state level.

1. Introduction

Carisoprodol (Soma®, Meda Pharmaceuticals Inc.), a skeletal muscle relaxant indicated for acute and painful musculoskeletal conditions, was initially approved as a non-controlled substance in the United States (US) in 1959 (SOMA [package insert], 2009). While experiments in the early 1960s did not identify addictive properties of carisoprodol (Fraser et al., 1961), over time, reports have described cases of abuse in various settings. In these cases, individuals typically used carisoprodol in much larger quantities than recommended to achieve mind-altering effects, to substitute for other, less-available drugs, or to potentiate the effects of co-ingested drugs (Reeves and Burke, 2010; Reeves et al., 2012). Concern about the abuse of carisoprodol, especially when

combined with other drugs such as opioids and benzodiazepines, continues to this day (Horsfall and Sprague, 2017; Losby et al., 2017).

The primary active metabolite of carisoprodol is meprobamate, a Schedule IV sedative-hypnotic (Olsen et al., 1994). In addition to the recognized abuse potential of meprobamate, recent studies suggest that carisoprodol itself can directly target the GABA_A receptor and produce a notable central nervous system depressant effect (Gonzalez et al., 2009a, b; Rho et al., 1997). At the population level, the significance of carisoprodol abuse has been demonstrated by findings from public surveillance systems. Among all drug abuse or misuse related emergency department (ED) visits across the US collected by the Drug Abuse Warning Network, the number of cases involving carisoprodol nearly doubled from 17,432 in 2004 to 29,864 in 2010 (Substance Abuse and

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Mental Health Services Administration, 2013). According to the National Survey on Drug Use and Health, the number of Americans 12 years and older using carisoprodol for non-medical purposes during their lifetime has been estimated to be around 3.3 million from 2013 to 2014 (Center for Behavioral Health Statistics and Quality, 2015).

Growing concerns over carisoprodol abuse have prompted regulatory actions. At the federal-level, a scheduling recommendation by the US Drug Enforcement Administration (DEA) in 1996 was unsuccessful because the Food and Drug Administration (FDA) Drug Abuse Advisory Committee concluded there was insufficient evidence to support controlling carisoprodol (Drug Enforcement Administration, 2009). At the state-level, where more restrictive pharmacy laws can be enacted, 21 states started to regulate carisoprodol as a controlled substance as early as 1994 (in New Mexico) (Fass, 2010; Reeves et al., 2012). A second attempt for federal action was made in 2009 when the DEA issued a Notice of Proposed Rulemaking to classify carisoprodol, which ultimately placed carisoprodol into Schedule IV, effective on January 11th, 2012 (Drug Enforcement Administration, 2011).

In the US, substances with abuse liability or addiction potential are regulated by the Controlled Substances Act (CSA) and are divided into five categories (schedules), with Schedule I being the most restrictive and Schedule V being the least restrictive (Controlled Substances Act, 1970; Rocha, 2013). Pursuant to the CSA, the intent of scheduling a prescription drug is to increase awareness of its abuse potential and curb overprescribing, to heighten the scrutiny over its distribution, and to prevent related controlled substance violations and criminal activities with the ultimate goal to reduce abuse, addiction, and overdose (Controlled Substances Act, 1970; Drug Enforcement Administration, 2011). Paramount to this legislative intent are studies that empirically test the policy's effectiveness, yet it remains unclear in the current literature how the clinical community and health systems have reacted to the potentially stronger message imposed by federal action and how use of carisoprodol was affected by the DEA Schedule IV classification.

We aimed to examine the effect of controlled substance designation on the dispensing of carisoprodol in a large commercially-insured population in the US.

2. Methods

2.1. Data source

We used data from the IBM MarketScan Commercial Claims and Encounters Database, which includes enrollment and billing records of a large national sample of beneficiaries (employees and their dependents, and retirees) with employer-sponsored health insurance from approximately 350 payers across the US (IBM Watson Health, 2018). The data sets contain person-level information on beneficiaries' demographics, diagnoses, and procedures associated with outpatient visits and inpatient stays, and outpatient-filled prescriptions. The analyses of this de-identified data set were exempted from review by the University of Florida Institutional Review Board.

2.2. Study design, time segments, and comparison groups

We used an interrupted time series (ITS) analysis, which is considered one of the strongest quasi-experimental designs for evaluating health policies (Bernal et al., 2017; Wagner et al., 2002). Compared to simple pre- and post-designs, ITS assesses the frequency of outcome measures multiple times before and after a timed intervention, thus reducing some threats (such as history and maturation) to internal validity (Penfold and Zhang, 2013).

The study period was divided into three time segments: (1) a 24-month pre-intervention period (November 2009 through November 2011) preceding the federal scheduling; (2) a 3-month intervention period (December 2011 through February 2012), encompassing the date when carisoprodol became officially a scheduled substance on

January 11th, 2012; and (3) a 24-month post-intervention period (February 2012 through February 2014). Because most policy implementations require some time until complete adoption, we omitted the 3-month intervention period from statistical analyses (Wagner et al., 2002).

We grouped states by whether or not a state had scheduled carisoprodol before the enactment of federal policy (Appendix Table S1*). Accordingly, 29 states with no scheduling prior to the 2012 federal policy (no-state-policy group) were compared to 17 states with state laws in place before 2010 (state-policy group). Most of these states had scheduled carisoprodol prior to 2004. We excluded four states (Mississippi, Tennessee, Washington, and Wyoming) that had classified carisoprodol as controlled substance between 2010 and 2011 because the impact of these prior state-level legislative efforts may confound the evaluation of federal scheduling enacted shortly thereafter.

2.3. Outcomes

Our unit of time measurement was one month. For each month, the eligible population included beneficiaries with medical and pharmacy benefits for the current and preceding 12 months. We then further restricted our study sample (denominators) to patients who had medical encounters with diagnoses indicating potential clinical need for muscle relaxants during the current or the preceding one month. These diagnoses included a broad range of musculoskeletal disorders: injury and related conditions, arthritis and related conditions, bone and spinal conditions, or tension headache (see Appendix Table S2* for detailed definitions).

We estimated (1) the proportion of eligible patients who filled at least one prescription for carisoprodol and (2) the proportion of eligible patients who newly filled (incident fill) carisoprodol each month. An incident fill was defined as having no carisoprodol fill in the preceding 12 months. The latter measure was introduced because patients with prescriptions that preceded federal scheduling could continue to fill these prescriptions. In contrast, carisoprodol initiation may be a measure more amenable to an immediate response by prescribers to the policy change.

In a sensitivity analysis, we lifted the requirement for musculoskeletal disorder diagnoses and explored the use of carisoprodol in a broader population which incorporated potential off-label use and use under less-established indications.

As an internal control series, we examined the dispensing of diazepam, which is also prescribed as a muscle relaxant, but maintained consistent Schedule IV designation throughout the study period. Doing so allowed us to rule out changes in carisoprodol prescribing that may have been related to other concurrent activities with focus on management of musculoskeletal disorders and pain. For example, increasing implementation of prescription drug monitoring programs across states may increase scrutiny of all controlled substance prescribing independent of other policy initiatives (Pauly et al., 2018).

2.4. Analysis

We first described the age, sex, geographic regions and types of musculoskeletal conditions for eligible patient-months before and after the federal scheduling. We then fitted segmented linear regression models to evaluate changes in the two outcomes of interest. In addition to the period indicator (pre- or post-federal scheduling), the month indicator, and the post-scheduling month indicator that are typically included in segmented linear regression models, we included a state indicator (0 for state-policy group and 1 for no-state-policy group) and interaction terms between this state indicator and the above-mentioned three indicators to test whether the effect of federal classification differed by existing state-level scheduling status (see appendix Table S3* for statistical equations). The linear trend function fitted the data well with all models having an R-square > 0.95.

Table 1
Study population characteristics for estimation of monthly carisoprodol dispensing.

Characteristic	No-state-policy group		State-policy group	
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Number of eligible patient-months	25,435,513	25,630,496	14,074,651	14,139,328
Age				
18–34	17.5%	18.2%	17.4%	18.2%
35–44	22.0%	21.1%	22.3%	21.8%
45–54	31.2%	30.3%	31.5%	30.4%
55–64	29.3%	30.4%	28.8%	29.6%
Sex (female)	60.4%	60.2%	61.2%	60.5%
Region				
Midwest	31.2%	30.5%	3.7%	3.8%
Northeast	36.7%	34.2%	12.5%	12.6%
South	12.6%	12.5%	69.6%	71.1%
West	19.5%	22.8%	14.2%	12.5%
Musculoskeletal conditions				
Injury and related conditions	19.4%	17.9%	13.6%	13.0%
Arthritis and related conditions	55.7%	57.1%	54.9%	55.6%
Bone and spinal conditions	53.2%	53.9%	58.0%	58.7%
Tension headache	0.8%	0.8%	1.0%	0.9%

We tested and accounted for clustering of observations across time (i.e., autocorrelation) by using the generalized Durbin-Watson test and included the appropriate autocorrelation orders in the final models. For ease of interpretation, we evaluated the impact of federal scheduling by calculating the relative difference between model-predicted (i.e., assuming pre-scheduling trends would have persisted) and observed outcomes during the first, second, third, and fourth 6-months periods, and the average over 2 years post-scheduling. In subgroup analyses, we explored whether the effect of federal scheduling varied across different age, sex, and musculoskeletal condition groups. All analyses were conducted with SAS version 9.4 (PROC AUTOREG command with NLAG function) and Microsoft Excel 2016.

3. Results

The eligible population consisted of 13.3 million beneficiaries with diagnosed musculoskeletal conditions and rendered approximately 79 million monthly observations over the study period. The majority of the study sample were middle aged women with arthritis and related conditions or bone and spinal conditions (Table 1). Patient-months in Southern states accounted for about 70% of the study sample in the state-policy group (i.e., 17 states that scheduled carisoprodol before 2010), whereas the Northeastern and Midwestern states made up about 70% of the no-state-policy group (i.e., 29 states with no state-level carisoprodol scheduling prior to the 2012 federal policy). There were no apparent changes in the distribution of age, sex, geographic regions, and types of musculoskeletal conditions of the eligible population between the pre- and post-intervention periods.

No-state-policy group had lower baseline prevalence of carisoprodol use (intercept: 11.0 vs. 21.1 patients with prescription fills per 1000 patients) as well as carisoprodol initiation (intercept: 4.5 vs. 7.2 patients with new prescription fills per 1000 patients) compared to the state-policy group (Table 2 and Fig. 1).

3.1. Changes in the prevalence of carisoprodol dispensing

During the pre-intervention period (Table 2 and Fig. 1), the prevalence of carisoprodol use remained relatively constant in the no-state-policy group, while it decreased steadily in the state-policy group (slope: 0.01 vs. –0.09 per 1000 patients per month; difference in slope between the groups: 0.10, $p < 0.01$). After the implementation of federal scheduling, the segmented regression model showed a significant, immediate decline in the prevalence of carisoprodol dispensing (–1.12 per 1000 patients, $p < 0.01$) and a significant change in

Table 2
Impact of federal Schedule IV controlled substance classification on monthly carisoprodol dispensing, parameters from the segmented linear regression.

Parameters	Any prescription fill ^a		New prescription fill ^b	
	Estimate	P value	Estimate	P value
Intercept (baseline use) ^c	21.11	< 0.01	7.22	< 0.01
Baseline trend ^c	–0.09	< 0.01	–0.05	< 0.01
Level change ^c	–1.12	< 0.01	–0.44	< 0.01
Trend change ^c	–0.07	0.02	–0.01	0.22
Difference in intercept ^d	–10.08	< 0.01	–2.74	< 0.01
Difference in baseline trend ^d	0.10	< 0.01	0.03	< 0.01
Difference in level change ^d	0.17	0.77	–0.07	0.72
Difference in trend change ^d	0.02	0.70	–0.007	0.61
R ² of the model	0.97		0.95	

^a Number of patients with any carisoprodol fill per 1000 patients.

^b Number of patients with an incident carisoprodol fill following 12 months without such fill per 1000 patients.

^c For states in the state-policy group.

^d Difference between states in the no-state-policy and state-policy group.

the slope (–0.07 per 1000 patients per month, $p < 0.02$). This effect was not modified by existing state-level scheduling status (difference in level change between no-state-policy and state-policy group: 0.17 per 1000 patients, $p = 0.77$; difference in trend change: 0.02 per 1000 patients per month, $p = 0.70$).

During the first, second, third and fourth 6-month periods following federal scheduling, the relative differences between observed and predicted (i.e., had carisoprodol utilization trends during the pre-intervention period persisted) carisoprodol use were 7.8%, 10.5%, 13.4%, and 19.8%. Averaged over two years, the difference was 12.3%.

3.2. Changes in carisoprodol initiation

Findings were similar for carisoprodol initiation (Table 2 and Fig. 1), which remained relatively constant in the no-state-policy group but was gradually decreasing in the state-policy group during the pre-intervention period (slope: –0.02 vs. –0.05 per 1000 patients per month; difference in slope: 0.03, $p < 0.01$). Federal scheduling was associated with a significant decline in the level (–0.44 per 1000 patients, $p < 0.01$) but not the trend of initiation (–0.01 per 1000 patients per month, $p = 0.22$).

During the first, second, third and fourth 6-month period following federal scheduling, the relative differences between observed and

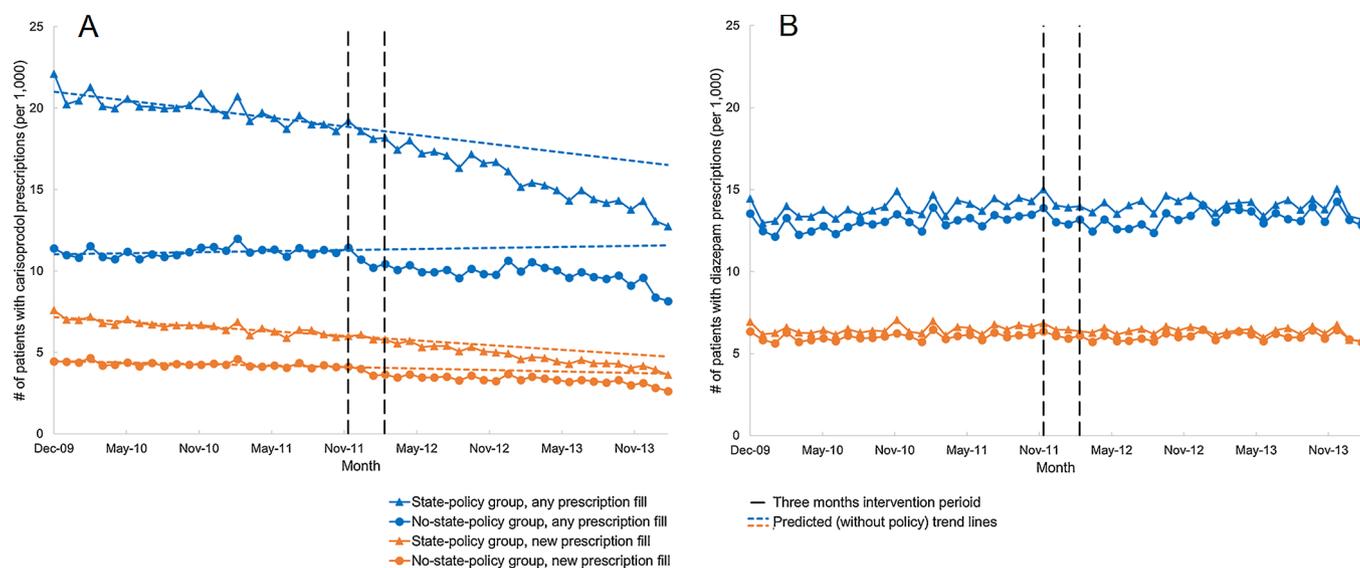


Fig. 1. Proportions of patients who filled/newly filled carisoprodol (A) or diazepam (B) each month. Classifying carisoprodol as a Schedule IV controlled substance at the federal level was associated with immediate declines in its dispensing (A). Meanwhile, the dispensing of diazepam remained relatively constant during the same time period (B).

predicted carisoprodol use were 8.3%, 11.2%, 13.1%, and 18.3%. Averaged over two years, the difference was 12.1%. Similar to what was observed in overall carisoprodol dispensing, the effect of federal scheduling on carisoprodol initiation was consistent between state groups without and with existing state-level carisoprodol scheduling (difference in level change: -0.07 per 1000 patients, $p = 0.72$; difference in trend change: -0.007 per 1000 patients per month, $p = 0.61$). By the end of the two-year observation period, carisoprodol initiation was avoided in approximately 21,000 patients (0.54 per 1000 patients).

3.3. Changes in carisoprodol dispensing across different subgroups

We observed a similar degree of reduction in the dispensing of carisoprodol among males and females. Between different age and clinical condition groups, the decline was more profound in younger patients (18–34 and 35–44 years for carisoprodol initiation, and 18–34 years for any carisoprodol dispensing) and patients with injury and related conditions (Table S4*).

3.4. Sensitivity analysis in the general population

In the sensitivity analysis that included all beneficiaries who met the continuous enrollment requirement, reductions in carisoprodol dispensing followed a similar pattern but to a slightly greater extent compared to the main analysis, which required appropriate indications. During 2 years after the implementation of federal policy, the relative difference between observed and predicted prevalence was both 15.5% for any carisoprodol prescription fill and 15.6% for incident carisoprodol prescription fills.

3.5. Changes in diazepam dispensing

Use of diazepam remained relatively constant during the entire study timeframe in both the no-state-policy and state-policy groups (Fig. 1). The segmented regression model did not identify significant changes in either level or slope of the prevalence, suggesting other interventions to address prescription drug abuse, such as prescription drug monitoring programs, were unlikely to explain the observed changes in carisoprodol dispensing.

4. Discussion

Numerous actions have been taken in recent years to curb the prescription drug abuse epidemic in the US. We found classifying carisoprodol as a Schedule IV controlled substance at the federal level was associated with moderate reductions in its dispensing, not only in states that newly adopted the classification but also in states where carisoprodol was previously scheduled by state laws.

Although the assessment of abuse potential is a critical component of New Drug Applications for psychoactive molecules (Food and Drug Administration, 2017), such knowledge may not always be available or accurate at the time of approval. Accumulated evidence of abuse in the real world may trigger the regulatory decision to add schedule to or change the schedule of marketed products, such as in recent cases of carisoprodol, hydrocodone combination products, and gabapentin (Drug Enforcement Administration, 2011; Kentucky Board of Pharmacy, 2017; Raji et al., 2018). Understanding the population-level impact of these regulations, including changes in prescribing patterns, will inform evidence-based policymaking to mitigate the harm associated with drug abuse and contribute to ongoing and future efforts to combat the prescription drug abuse epidemic.

To date, evidence demonstrating the effect of regulatory actions against carisoprodol has primarily originated from Norway, where, similar to regulatory action in other European countries, carisoprodol was placed into the highest scheduling level (class A) in 2007 and was subsequently withdrawn from the market in 2008 (Bramness et al., 2008). A study found use of carisoprodol decreased substantially (from 53,116 to 10,679 users) comparing the two 9-month periods before and after rescheduling (Bramness et al., 2012). Carisoprodol-involved driving under the influence cases and forensic autopsy cases also decreased (Hoiseith et al., 2009). Compared to Norway, the US has a more complex system that places controlled substances into one of the five categories based on their medicinal value, harmfulness, and potential for abuse or addiction (21 U.S.C. § 812). Schedule II is the highest possible category in which a prescription drug may be placed. Because drugs under this category are subject to the most stringent regulations, the decision to reschedule is expected to have a direct impact, as shown in several recent studies in which the utilization of hydrocodone combination products decreased substantially after a reclassification from Schedule III to Schedule II (Jones et al., 2016; Oehler et al., 2016; Raji et al., 2018; Schultz et al., 2016; Tran et al., 2017).

However, there is a lack of understanding of how the least restrictive type of scheduling (from non-scheduled to Schedule IV) might influence drug use and associated misuse/abuse cases. Relative to the Schedule II, the CSA imposes less restrictive regulations for drugs in lower categories, which may have limited impact. For example, a Schedule II controlled substance cannot be refilled, while a Schedule III to IV controlled substance may be refilled up to five times within six months (21 U.S.C. § 829). We identified two studies, both suggesting that adding a drug to Schedule IV decreased related drug poisoning cases (Spiller et al., 2010; Sun et al., 2018). In a study of tramadol, authors noted a decrease of tramadol poisoning cases in two scheduled states but a continued increase in two control states (Spiller et al., 2010). In another study, the number of phone calls received by the California Poison Control System for carisoprodol abuse or misuse fell from 994 to 652 during the four years before and after the 2012 federal policy (Sun et al., 2018). Decreased access to carisoprodol through prescriptions, as suggested by our study, is consistent with the observed decrease in poisoning cases.

Reasons underlying the decline in carisoprodol use are likely multifactorial. At the individual level, public discussions and debates surrounding the regulatory action and subsequent controlled substance designation may increase prescribers' awareness of carisoprodol's abuse potential, leading to prescribing behavior change. According to a survey (n = 154), 64.3% of physicians indicated that scheduling a substance had a negative impact on their willingness to prescribe (Parker and Larrat, 2009). At the system level, some health plans started to add restrictions for carisoprodol prescribing or to eliminate carisoprodol from the formulary, which further limited access to carisoprodol on a larger scale (Inland Empire Health Plan, 2016; Drugs.com, 2011). Our study does not elucidate such mechanisms of policy uptake and adoption but may generate hypotheses for future research.

Before the federal scheduling, use of carisoprodol was gradually decreasing in the state-policy group but remained relatively constant in the no-state-policy group, which may be explained by the existing state-level control substance designation. After the federal scheduling, we found use of carisoprodol not only decreased in states without control substance designation but also decreased, and to the same extent in states with the state-level designation. This effect likely reflects an increased awareness of abuse reinforced by the federal scheduling and aforementioned changes at the system level (e.g., health plan formularies), which is beyond the pure effect of CSA imposed regulations towards prescribing and dispensing of a Schedule IV controlled substance *per se*.

The more pronounced effect of scheduling in certain patient groups may be attributed to closer scrutiny by prescribers. For example, the young age group had the highest prevalence of substance use issues (Center for Behavioral Health Statistics and Quality, 2015). While the injury and related conditions are acute in nature, prescribers may be more likely to choose other non-controlled muscle relaxants. In cases of off-label use and use under less established indications, prescribers may exercise greater caution.

Considering the comparably lenient regulations governing the distribution and dispensation of Schedule IV prescription drugs, it is not surprising the scheduling only resulted in a moderate 20% decrease in carisoprodol dispensing after two years compared to about 80% decrease in nine months in Norway. Given that several alternative agents exist in the same therapeutic class which can substitute carisoprodol, it is feasible to consider placing carisoprodol into a more restrictive category. In fact, carisoprodol was placed in Schedule II of the Louisiana Uniform Controlled Substances Law in 2014 (Louisiana Board of Pharmacy, 2014).

Our study has limitations. First, the commercially-insured population is not representative of the entire US population; as such, our results may not be generalizable to other populations such as beneficiaries covered by public insurance. Second, prescription claims

reflect only dispensing data and allow no inferences about the intent of prescribing. Also, our datasets cannot capture prescriptions paid entirely by cash or obtained from non-medical sources. Third, despite the use of the strongest quasi-experimental design, other concurrent interventions may have had an influence on the utilization of carisoprodol. We partially accounted for this possibility by examining a related but different outcome (i.e., use of diazepam). Moreover, the fact that carisoprodol prescriptions declined immediately after the intervention is more suggestive of a causal association.

5. Conclusion

Schedule IV controlled substance classification at the federal level was associated with a moderate decrease in the dispensing of carisoprodol, regardless of previous controlled substance designation at the state level. Declines in utilization were most pronounced among younger age groups and patients with injuries. Future studies should evaluate whether further restriction is needed to ensure safe and effective treatment of musculoskeletal pain.

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Contributors

YL conceived and designed the study, and CD, JB and AW helped refine the study design. YL conducted the analysis, and all authors assisted with interpretation of results. YL drafted the manuscript, and all authors revised and finalized the paper. AW supervised the study. All authors have approved the final manuscript.

Conflicts of interest

This study was presented at the 34th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, August 2018, Prague, Czech Republic.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugalcdep.2019.05.025>.

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