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Efe Eworuke
Food and Drug Administration, efe.eworuke@fda.hhs.gov

Joo-Yeon Lee
Food and Drug Administration

Lisa Soule
Food and Drug Administration

Vaishali Popat
Food and Drug Administration

David G. Moeny
Food and Drug Administration

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ORIGINAL REPORT

The impact of the boxed warning on the duration of use for depot medroxprogesterone acetate

Efe Eworuke[1]*, Joo-Yeon Lee[2], Lisa Soule[3], Vaishali Popat[4] and David G. Moeny[1]

[1] *Division of Epidemiology II, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MA, USA*
[2] *Division of Biometrics VII, Office of Biostatistics, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MA, USA*
[3] *Division of Bone, Reproductive, and Urologic Products, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MA, USA*
[4] *Office of New Drugs, Immediate Office, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MA, USA*

ABSTRACT

Objective The objective of this study was to examine the impact of the Food and Drug Administration's boxed warning on the utilization of depot medroxyprogesterone (DMPA).

Methods From the IMS Lifelink data (2001–2009), we identified DMPA and oral combined hormonal contraceptive (CHC) users without a prescription claim 6 months before and after the first and last claim. Episodes were defined as all contiguous claims with no more than 90-day DMPA or 30-day CHC between claims. Days' supply (CHC) and 90-day duration (DMPA) was used to determine episodes. We used interrupted time series to evaluate changes in the mean episode length and proportion of episodes >2 years before and after the Food and Drug Administration's November 2004 boxed warning. Stratified analyses by birth cohort were conducted.

Results From 2001 to 2009, 126 528 DMPA and 651 356 CHC episodes were used for segmented regression. For the DMPA cohort, there was an immediate decline in the mean duration (−34.7 days [confidence interval: −45.4 to −24.1]) and episodes >2 years (−1.9% [confidence interval: −2.9% to −1.1%]) after the boxed warning. We did not observe any change in mean duration or episodes >2 years for the CHC cohort. The largest declines in mean duration and proportion >2 years were seen with the oldest women.

Conclusion We observed a modest decline in the mean duration and episodes >2 years for DMPA use immediately after the boxed warning not observed among CHC users. In the stratified analysis, we saw declines in the duration of use >2 years in all age groups, except adolescents who continue to use DMPA for longer than 2 years. Published 2017. This article is a U.S. Government work and is in the public domain in the USA.

KEY WORDS—boxed warning; depot medroxyprogesterone; interrupted time series; trends; pharmacoepidemiology

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INTRODUCTION

The US Food and Drug Administration (FDA) approved depot medroxyprogesterone acetate (DMPA; Depo-Provera contraceptive injection) in October 1992[1] and subcutaneous depot medroxyprogesterone (depo-subQ provera 104) in October 2004[2] for the prevention of pregnancy. Depo-subQ provera 104 is also approved for management of endometriosis-associated pain. DMPA results in decreased estrogen production because of its inhibition of pituitary gonadotropin secretion.[3] Decreased estrogen production is particularly concerning because it is associated with decreases in bone mineral density (BMD). Shortly after approval of DMPA in 1992, postmarketing studies[4–11] in both adult and adolescent women suggested loss of BMD with DMPA use. Longer duration of treatment and smoking tobacco were associated with slower recovery of BMD following the last DMPA use.[12] Another study[6] suggested that BMD levels at the femoral neck and hip showed slower

*Correspondence to: E. Eworuke, Division of Epidemiology II, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration,10903 New Hampshire Ave Bldg. 22, Silver Spring, MA, USA. E-mail: efe.eworuke@fda.hhs.gov

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recovery compared with levels at the lumbar spine after treatment discontinuation. In 2004, the FDA approved a boxed warning to communicate these risks. Boxed warnings are used when there is a serious adverse reaction (in this case, loss of BMD) that can be prevented or reduced in frequency or severity by appropriate use of the drug (i.e., limiting duration of use) to ensure safe use. The initial boxed warning in 2004 and its subsequent revision in 2010 were based on FDA's review of clinical data submitted by the sponsor, the findings of the postmarketing study[13] and another observational study.[14] The current boxed warning states that DMPA may result in significant BMD loss, which is greater with increasing duration of use and may not be completely reversible, and that it is not known if contraceptive use during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture later in life. And lastly, labeling states that DMPA injection should only be used as long-term birth control (i.e., longer than 2 years) if other methods are inadequate.

Shortly after the boxed warning, several public organizations including the World Health Organization,[15] the American College of Obstetricians and Gynecologists,[16] and the Society of Adolescent Medicine[17] indicated that skeletal health concerns should not restrict DMPA use including duration of use. With conflicting guidance from professional organizations and from the FDA, it is unknown how prescribers would react to the boxed warning. Currently, evaluation of the impact of the boxed warning and published guidelines on DMPA prescribing is limited to a Florida survey[18] conducted among obstetrician-gynecologists. The study revealed that 46% of these physicians place a 2-year time limit on DMPA use, and more than half of the respondents report that they instituted this time limit because of the boxed warning. Small sample size, volunteer bias, recall bias, and limited generalizability of the study population preclude generalizing these survey findings to other practitioners in the USA. With several public organizations releasing statements against the warning, coupled with existing evidence limited to only one survey, we sought to examine changes in the trends of DMPA use because of the boxed warning issued in November 2004 in a large commercial database.

METHODS

Data source

We obtained data from the IMS Health LifeLink dataset. The dataset consists of fully adjudicated medical, pharmacy, and enrollment information from over 100 managed care plans. Key data elements include costs, diagnoses, prescription drugs, services rendered across all sites of care, and patient demographic information. IMS LifeLink data provide patient-level data for over 65.8 million individuals for health services initiated across the USA.

Study population

We identified DMPA users as patients from the 2001–2013 IMS LifeLink dataset, who received a prescription for subcutaneous or intramuscular DMPA through a pharmacy, those with a procedure code for the administration of DMPA at the physician's office (J1051, J1055, J1056, J1050), or patients with a procedure code for the administration of an unclassified drug (J3490) with a corresponding prescription claim for DMPA on the same day. We refer to this sample as DMPA users. From the source population, we identified users of oral formulations of combined hormonal contraceptives (CHCs) as an active comparator. Patients with a pharmacy prescription claim for any oral CHC were included. We excluded from the CHC population women who used DMPA during the study period to select women who were less likely to switch from DMPA to CHC. We refer to this sample as CHC users.

To create the final DMPA study population, we restricted DMPA users to patients with year of birth 1963–2001 (representative of child-bearing age), with at least 6 months of continuous enrollment prior to the first DMPA medical or pharmacy claim and at least 6 months of continuous enrollment after the last DMPA claim. The same enrollment criteria were used to create the final CHC study population.

Episode construction

All pharmacy and medical claims for DMPA between the first and last DMPA claims were retrieved and used to construct the episodes of DMPA use. Each episode began with the first DMPA claim or a subsequent DMPA claim and included all DMPA claims that had no more than a 90-day gap period between claims. The duration of DMPA exposure following administration was defined as 90 days in accordance with the product labeling. Therefore, the presence of another claim before the 90-day defined duration resulted in an overlap between prescription claims, which was excluded from the analysis. This criterion was applied because we assumed data entry errors for earlier injection administration before the 90-day period. In a sensitivity analysis, we changed

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the 90-day gap between claims to 75 and 105 days to reflect early or later injection as observed in clinical practice. For the CHC episodes, we relied on the pharmacy-calculated days' supply to determine the duration of episode. Given that overlap days for the CHC user increased exposure time, overlap days were added to the episode length and not excluded. The length of the episode duration (in days) was calculated for all episodes constructed in both cohorts. After the episodes were created, we mapped all the episodes by calendar month. In each calendar month, the lengths of all episodes were used to calculate the mean episode length in days (we refer to this as mean duration) for the month and the proportion of patients (expressed as percent) who have episodes of use greater than 730 days (we refer to this as proportion >2 years). We used only the first DMPA and CHC episodes and obtained both the mean duration and proportion >2 years for each start month of DMPA or CHC prescription.

ANALYSIS

Interrupted time series

Interrupted time series (ITS) was applied to assess the impact of the boxed warning issued in November 2004. Two endpoints, which are the mean duration and the proportion >2 years, were analyzed separately in terms of monthly trends and change in trend before and after the boxed warning. To ensure that the trends observed using the DMPA cohort were not attributed to study sample definitions and to confirm that findings were unique to DMPA, we conducted the same analyses among CHC users. The ITS design with a control group is a valid quasi-experimental study able to estimate intervention effects (e.g., policy implementation) in non-randomized settings.[19] In contrast to pre-post designs, ITS uses multiple assessments of the outcome variable before and after the intervention, thus reducing the threats (such as history and maturation) to the internal validity of the study.[19]

The data for ITS analysis were restricted to July 2001 (because of limited data from January 2001 to June 2001) to December 2009 (to assure ample follow-up time). In the final model, the baseline trend estimated the trend for mean monthly duration or proportions before the boxed warning; level change estimated the change immediately after the warning, and trend change estimated the change in slope (trend) before and after the boxed warning. Stratified analyses by birth year strata (1963–1972, 1973–1977, 1978–1982, 1983–1987, >1987) and concurrent CHC use were also conducted to examine differences in trends by strata. All regressions were performed using the PROC AUTOREG procedure within SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). Autocorrelation between error terms was assessed using the Durbin–Waston test statistic. Models were assessed by looking at various model diagnostics such as residual plots and autocorrelation factor (ACF)/partial autocorrelation factor (PACF) function. In a sensitivity analysis, we excluded all episodes that were initiated prior to 1 January 2004 and ended between 1 January 2004 and 31 December 2004 to exclude episodes possibly terminated because of the implementation of the boxed warning. The study was exempted from review by the FDA Research Involving Human Subjects committee under 45 CFR 46 101(b)(4).

RESULTS

We identified 659 783 DMPA users from January 2001 to December 2013. Further restrictions requiring enrollment information in the 6 months prior to first DMPA use and continuous enrollment after last DMPA use resulted in a sample of 191 927 users. Finally, we restricted to women born between 1963 and 2001 to increase the likelihood that DMPA use was indicative of contraception (Figure 1). The same criteria were applied to the CHC cohort. The final sample included 517 801 DMPA claims for 179 108 women and 5 989 949 CHC claims for 845 189 women. This created 203 477 DMPA and 1 309 298 CHC episodes from the final sample. The ITS analysis (analytical cohort) included a total of 126 528 and 651 356 DMPA and CHC new users, respectively, between July 2001 and December 2009.

A summary of selected characteristics summarized in Table 1 contrasts the DMPA and CHC users for the analytical cohort. DMPA users were younger, more likely born after 1987 (25.1%) compared with CHC users who were older, more likely born between 1963 and 1972 (24.3%). The regional distribution for DMPA and CHC users was similar. Most of the women were in the Midwest region followed by the South region for both cohorts. We observed only a small proportion (10.2%) of DMPA users concurrently used a CHC during their DMPA use compared with those who used a CHC before first DMPA use (15.7%) or after last DMPA use (20.1%). Further evaluation of the 10.3% of overlapping episodes revealed that 84.7% (n = 15; 271 episodes) had a CHC claim that occurred within 30 days of the episode end date (n = 13; 972 episodes) or episode start date (n = 2; 183 episodes) suggesting a possible switch at the beginning or end of the DMPA episode. These data

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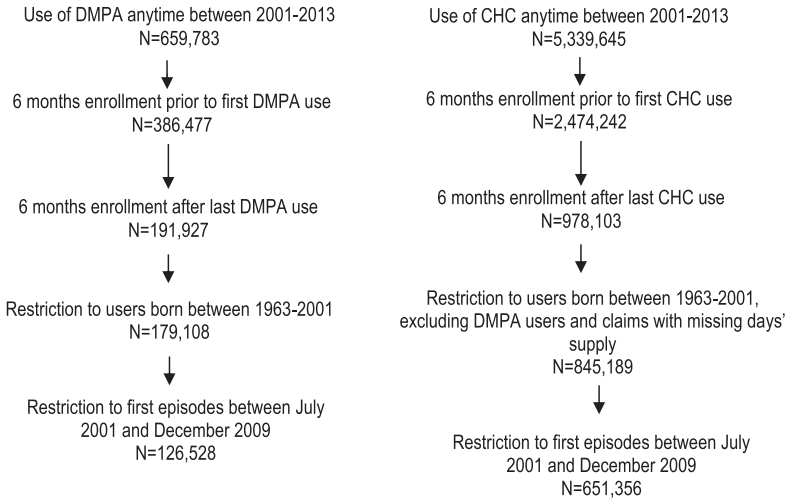

Figure 1. Flow chart deriving the final study cohorts. DMPA, depot medroxyprogesterone acetate; CHC, combined hormonal contraceptive

Table 1. Selected characteristics of DMPA and CHC new users

	DMPA new users		CHC new users	
Characteristic	*n* = 126 528	%	*n* = 651 356	%
Birth year				
1963–1972	24 362	19.3	156 856	24.1
1973–1977	17 643	13.9	108 931	16.7
1978–1982	23 799	18.8	123 717	19.0
1983–1987	28 166	22.3	132 423	20.3
>1987	32 302	25.6	127 694	19.7
Region				
East	23 455	18.5	128 450	19.7
Midwest	48 451	38.3	232 805	35.7
South	32 780	25.9	176 891	27.2
West	21 842	17.3	113 210	17.4
CHC use during first DMPA episode	12 972	10.3	NA	NA
CHC use in the 6 months prior to first DMPA use	19 915	15.7	NA	NA
CHC use in the 6 months after last DMPA use	26 027	20.6	NA	NA

DMPA, depot medroxyprogesterone acetate; CHC, combined hormonal contraceptive; NA, not applicable.

indicate that while there may be possible overlapping DMPA and CHC use, the probability of this occurrence is quite low.

The number of new users each month increased over time for both the DMPA and CHC cohorts and declined in the final months of the study period (Figure 2a). Both cohorts displayed similar time trends over time with a distinct increase in the number of new users in June 2003. The same spike in the number of new users was also observed when we examined the number of users each month (Figure 2b).

Examining the duration of use, we found that the monthly mean duration (−34.7 days [confidence interval (CI): −45.4 to −24.1; $p < 0.0001$]) and the proportion >2 years (−1.9% [CI: −2.9 to −1.1; $p < 0.0001$]) significantly reduced right after the boxed warning for the DMPA cohort only (Figure 3a and b). We did not observe a level change after the warning in the CHC cohort for both mean duration and proportion >2 years, although the trend change was significant for both the mean duration and proportion >2 years for both cohorts (Table 2).

For the stratified analysis by birth cohort, we excluded 282 and 1914 DMPA and CHC users, respectively, because the estimated age at index date was <11 years. Examining DMPA utilization by birth cohorts suggests differences by age. Prior to the boxed warning, all birth cohorts for DMPA users exhibited significant increasing baseline trend for the monthly mean duration (Table 3). Using the proportion >2 years as the endpoint, we also observed similar baseline trends across birth cohorts except for the post-1987 birth cohort, which exhibited a significant "downward" baseline trend prior to the boxed warning (−0.6% [CI:−0.4% to −0.8%]). The baseline trend for monthly mean duration for the CHC birth cohorts was not statistically significant except for the 1978–1982 and post-1987 birth cohorts. Although we found statistically significant increases in the baseline trends for proportion >2 years among the CHC birth cohorts prior to the boxed warning, the magnitude of the slopes was smaller than that observed in the DMPA birth cohorts (Table 3).

Except for the post-1987 and 1978–1982 birth cohorts, we observed significant declines in the mean

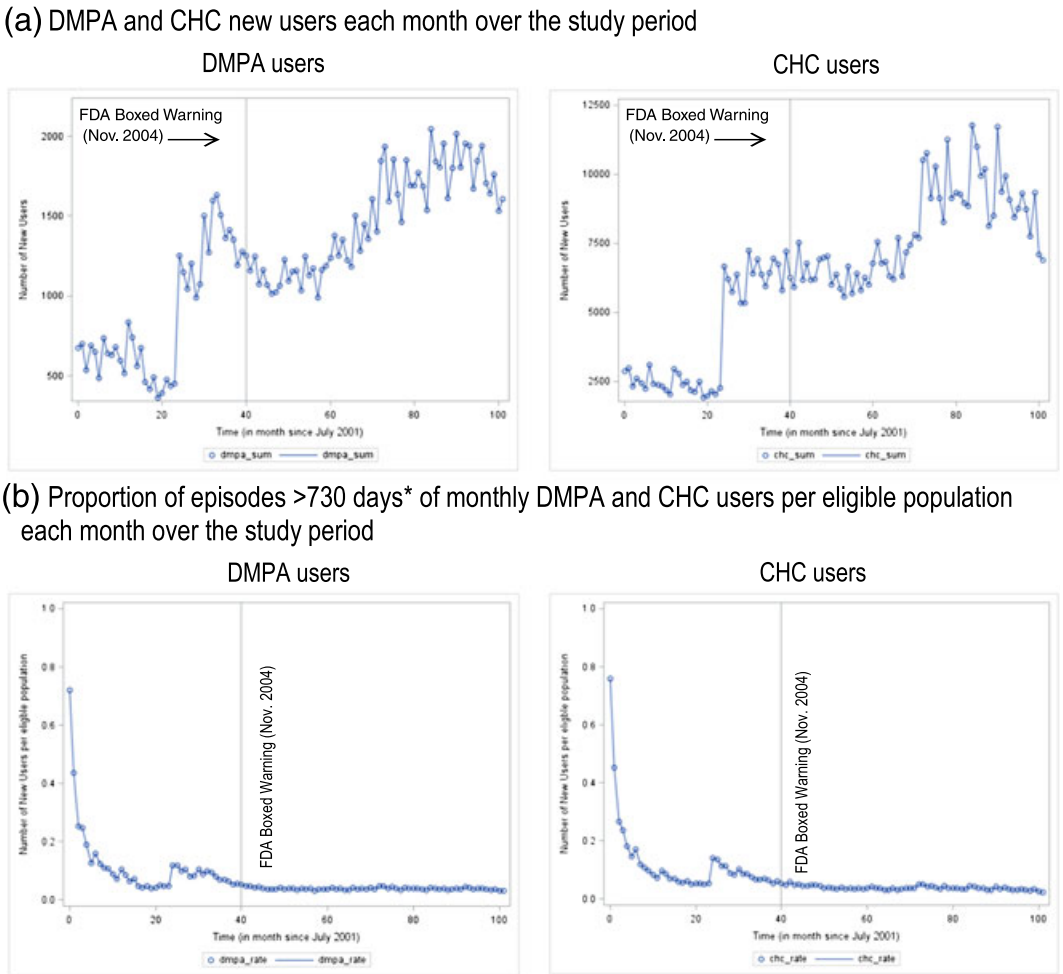

Figure 2. (a) Depot medroxyprogesterone acetate (DMPA) and combined hormonal contraceptive (CHC) new users each month over the study period. (b) Proportion of episodes >730 days* of monthly DMPA and CHC users per eligible population each month over the study period. The numerator is the number of new users in the month of interest, while the denominator includes the number of women included in the study based on cohort entry requirements. At the initial study months, the denominator comprises mainly of new users (large percent of new users per eligible population). However over time, the denominator comprises of prevalent users with a steady rate of new users. *Calculated as the number of subjects >730 days/total number of subjects who initiated DMPA in each month. [Colour figure can be viewed at wileyonlinelibrary.com]

duration and proportion >2 years for all DMPA birth cohorts immediately after the boxed warning (level change) (Table 3). For the >1987 cohort, we observed a non-significant increase in level change for proportion >2 years (3.7% [CI: 8.6% to −1.2%]) and a decline (non-significant) for 1978–1982 birth cohort (−1.2% [CI: −2.5% to 0.1%]) (Table 3). Statistical significance was not achieved in the CHC stratified birth cohorts, except for 1983–1987 birth cohort (Table 3). For the DMPA birth cohorts, the magnitude of the level change also varied by birth cohort, the oldest (1963–1972) (−55.0 days [CI: −35.7 to −74.4]) and youngest women (post-1987) (−43.1 days [CI: −24.9 to −61.3]) exhibited the largest decline. Except for the post-1987 birth cohort, the mean duration "level change" observed in the DMPA birth cohorts accompanied a decline in percent of episodes >2 years. Older women (1963–1972) (−3.7% [CI: −2.5% to −4.8%]) exhibited the largest decline in magnitude. For the youngest birth cohort, although there was a decline in the mean duration, we observed no level change for proportion >2 years (Table 3).

The difference in the slopes before and after the boxed warning (trend change) for both the mean duration and proportion >2 years was significant in all DMPA birth cohorts. The trends in the CHC birth cohorts were less consistent; some of the birth cohorts (1963–1972 and 1983–1987) showed no difference in monthly mean duration trend pre-boxed and post-boxed warning, while the remaining CHC birth cohorts had a significant trend change (Table 3).

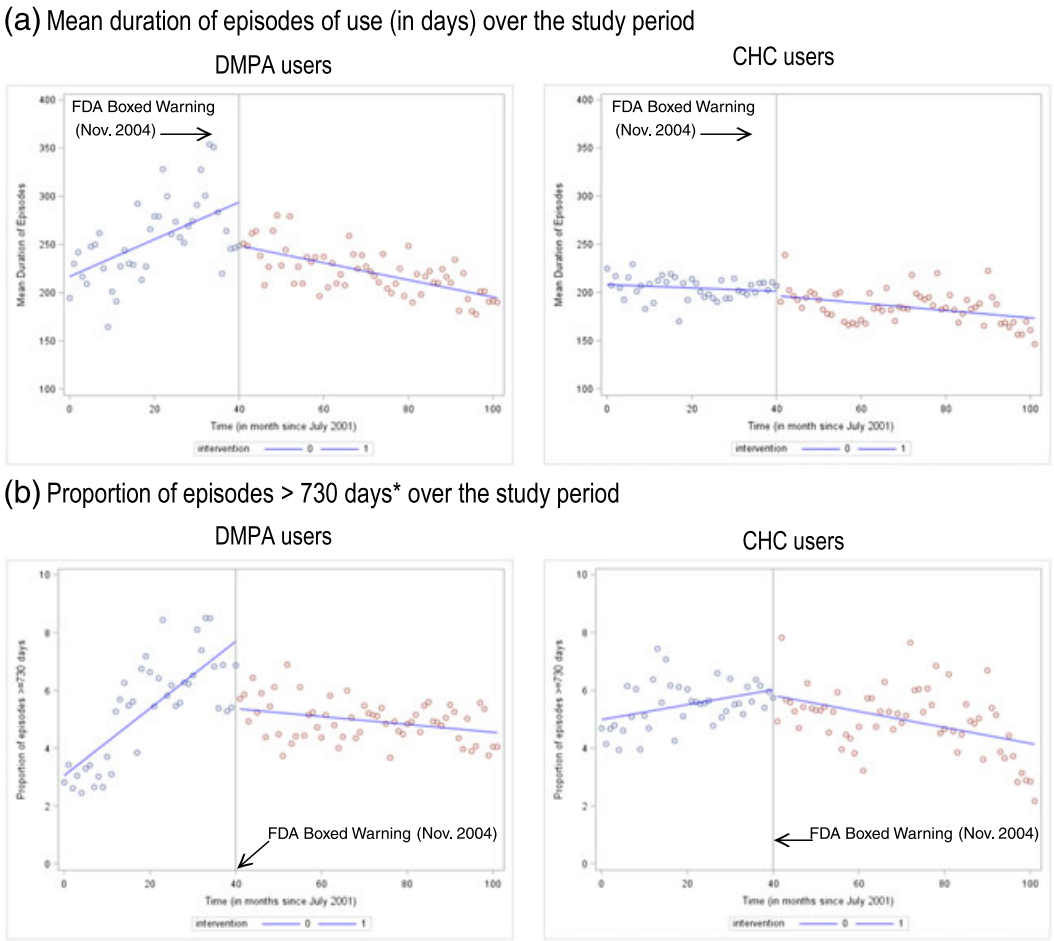

Figure 3. (a) Mean duration of episodes of use (in days) over the study period. For all episodes initiated in the respective month, the mean duration of episode was calculated for both Depot medroxyprogesterone acetate (DMPA) and combined hormonal contraceptive (CHC) cohorts. *Y*-axis represents the calculated mean for each calendar month, and *X*-axis represents the number of months since July 2001 till December 2009. (b) Proportion of episodes >730 days* over the study period. For all episodes initiated in the respective month, the proportion of episode with days >730 of all episodes that month was calculated for both DMPA and CHC cohorts. *Y*-axis represents the calculated mean for each calendar month, and *X*-axis represents the number of months since July 2001 till December 2009. *Calculated as the number of subjects >730 days/total number of subjects who initiated DMPA in each month 100. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 2. Interrupted time series analysis and confidence intervals for DMPA and CHC new users

	Variable	Estimate	LCL	UCL	*p*-value	Estimate	LCL	UCL	*p*-value
Model		DMPA				CHC			
Model 1 (mean in days)	Intercept	208.9	200.8	217.1	<.0001	196.5	189.3	203.8	<.0001
	Baseline trend	1.9	1.5	2.2	<.0001	0.27	−0.05	0.6	0.0985
	Level change	−34.7	−45.4	−24.1	<.0001	−3.4	−12.6	5.9	0.4754
	Trend change	−2.3	−2.7	−1.9	<.0001	−0.6	−0.96	−0.2	0.0016
Model 2 (proportions*)	Intercept	3.1	2.4	3.8	<.0001	4.5	3.97	5.0	<.0001
	Baseline trend	0.1	0.08	0.2	<.0001	0.04	0.02	0.07	0.0003
	Level change	−1.9	−2.9	−1.1	<.0001	−0.3	−0.94	0.3	0.3576
	Trend change	−0.1	−0.2	−0.09	<.0001	−0.07	−0.09	−0.04	<.0001

DMPA, depot medroxyprogesterone acetate; CHC, combined hormonal contraceptive; LCL, lower confidence interval; UCL, upper confidence interval. Baseline trend represents the estimated trend for mean monthly duration or proportions before the boxed warning; level change represents the estimated change immediately after the warning, and trend change represents the estimated change in slope (trend) before and after the boxed warning.
*Calculated as the number of subjects >730 days/total number of subjects who initiated DMPA in each month multiplied by 100.

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Table 3. Interrupted time series analysis and confidence intervals for DMPA and CHC new users stratified by birth year

Model parameter estimates using monthly mean duration (in days)								
Birth Year Cohort	Intercept		Baseline trend		Level change		Trend change	
	DMPA	CHC	DMPA	CHC	DMPA	CHC	DMPA	CHC
1963–1972	211 (225.8 to 196.3)	208.8 (219.5 to 198)	2.3 (3 to 1.7)	−0.2 (0.2 to −0.7)	−55 (−35.7 to −74.4)	−3 (10.8 to −16.7)	−3.2 (−2.4 to −3.9)	−0.2 (0.3 to −0.7)
1973–1977	215.7 (226.7 to 204.7)	192.2 (200.1 to 184.2)	1.3 (1.8 to 0.8)	0.3 (0.6 to −0.1)	−29.8 (−15.3 to −44.2)	−3.4 (7 to −13.7)	−1.8 (−1.3 to −2.4)	−0.8 (−0.4 to −1.2)
1978–1982	193.5 (205.1 to 181.9)	166.6 (174 to 159.3)	1.7 (2.2 to 1.2)	0.9 (1.3 to 0.6)	−20.2 (−5.1 to −35.2)	1.8 (11.3 to −7.7)	−2.1 (−1.5 to −2.6)	−1.4 (−1 to −1.8)
1983–1987	230.2 (243.7 to 216.7)	214.8 (225.1 to 204.5)	0.9 (1.5 to 0.3)	0 (0.5 to −0.4)	−33.9 (−16.8 to −51.1)	−17.2 (−4.1 to −30.3)	−1.3 (−0.6 to −2)	−0.5 (−1 to 0.1)
>1987	235 (249 to 220.9)	153.2 (168.8 to 137.7)	2.8 (3.5 to 2.2)	2.7 (3.4 to 2)	−43.1 (−24.9 to −61.3)	−19.2 (−39.6 to 1.2)	−4 (−3.3 to −4.6)	−3.3 (−2.5 to −4)
Model parameter estimates using monthly proportion of episodes >730 days (in percent)								
1963–1972	3.2 (4.1 to 2.4)	4.9 (5.6 to 4.2)	0.2 (0.2 to 0.1)	0 (0.1 to 0)	−3.7 (−2.5 to −4.8)	−0.2 (0.7 to −1.1)	−0.2 (−0.1 to −0.2)	−0.1 (0 to −0.1)
1973–1977	3.5 (4.6 to 2.5)	3.9 (4.4 to 3.4)	0.1 (0.1 to 0)	0.1 (0.1 to 0)	−1.9 (−0.5 to −3.2)	−0.7 (−0.1 to −1.3)	−0.1 (0 to −0.1)	−0.1 (−0.1 to −0.1)
1978–1982	2.3 (3.3 to 1.3)	3.4 (3.9 to 2.9)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0)	−1.2 (−2.5 to 0.1)	0 (0.7 to −0.7)	−0.1 (0 to −0.2)	−0.1 (−0.1 to −0.1)
1983–1987	3.4 (4.5 to 2.3)	5.9 (6.8 to 5)	0.1 (0.1 to 0.1)	0 (0 to 0)	−2.5 (−1.1 to −3.9)	−1.1 (−0.1 to −2.1)	−0.1 (0 to −0.2)	0 (0 to 0)
>1987	27.5 (33.8 to 21.3)	4.6 (5.8 to 3.4)	−0.6 (−0.4 to −0.8)	0.1 (0.1 to 0.1)	3.7 (8.6 to −1.2)	−0.3 (0.9 to −1.6)	0.5 (0.8 to 0.2)	−0.1 (0 to −0.2)

DMPA, depot medroxyprogesterone acetate; CHC, combined hormonal contraceptive.
Proportions were calculated as the number of subjects >730 days/total number of subjects who initiated DMPA in each month 100.
Baseline trend represents the estimated trend for mean monthly duration or proportions before the boxed warning; level change represents the estimated change immediately after the warning, and trend change represents the estimated change in slope (trend) before and after the boxed warning.

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For the stratified analysis by concurrent CHC status, DMPA utilization patterns remained the same among women who used concurrent CHCs during DMPA episodes and those who did not (Table 4). The magnitude of level change for mean duration for non-concurrent DMPA-contraceptive users was smaller (−18.9; CI: −35.3 to −2.5) compared with concurrent users (−36.5; CI: −47.6 to −25.5) (Table 4). Similarly, baseline trend (non-concurrent: 1.3; concurrent: 1.93) and trend change (non-concurrent: −1.6; concurrent: −2.4) followed the same pattern. Sensitivity analyses based on 75 or 105 days between DMPA claims (rather than 90 days) did not change our results (Appendix). Other sensitivity analyses, excluding DMPA episodes initiated before 1 January 2004 and ended between 1 January 2004 and 31 December 2004, also did not change our study findings.

DISCUSSION

In our study, we found a significant decline in the monthly mean duration of use and proportion of patients who have episodes of use greater than 730 days immediately after the boxed warning for the DMPA cohort; this was not seen in the CHC cohort. The observed pattern of utilization was not associated with a change in the number of users as we found comparable time trends for monthly new users in both the DMPA and CHC cohorts with no noticeable change after the boxed warning. This finding highlights the effectiveness of the FDA warning in limiting prolonged use of DMPA and not necessarily the change in the number of new users over the study period.

We examined whether prescribers were complying with the 2-year recommendation using two different analytical approaches. Using the episode of continuous use, we first assessed whether the mean duration of episodes changed significantly after the boxed warning. We observed significant changes in the mean duration, which was not found among CHC users. The analysis of the proportion >2 years examining the percent change in the proportion of episodes >2 years resulted in similar findings. Specifically, for DMPA users, there was a significant decline in level change for monthly mean duration and proportion >2 years. On the contrary, the CHC cohort exhibited no level change in the monthly mean duration and proportions immediately after boxed warning. The DMPA cohort also exhibited a significant difference in the trend change post-boxed warning. Among the CHC users, we also found a significant trend change similar to DMPA users. We were unclear why there would be a difference in the slopes before and after the boxed warning for the CHC cohort, given the absence of a level change. One possible explanation is the decline in the number of users for both cohorts toward the end of the study period. It is noteworthy to mention that our analysis was truncated at December 2009 to reduce this problem; however, as seen in Figure 2, we begin to see a drop in sample size prior to December 2009.

Stratified analyses suggest differences in duration of use by age. The largest decline in the mean duration in the DMPA cohort after the implementation of the boxed warning was observed among the oldest (1963–1972 birth cohort) and the youngest cohorts (post-1987 birth cohort). While a similar decrease was observed with the proportion >2 years for the older cohort, this trend was not replicated in among the younger women. The magnitude of level change also seemed to decrease with decreasing age (Table 3). These distinct differences by birth cohort may reflect clinical practice decisions; oldest and youngest patients perceived as having a higher risk of BMD loss may have been more likely to receive DMPA for a shorter duration following the warning, hence the decline in level change and trend change. The absence of a decline in the proportion of patients with episodes >730 days for the youngest cohort suggests that the number of women who received DMPA for >730 days remained constant during the study period. While the mean duration is sensitive to any change in duration, the proportion of episodes >730 days reflect

Table 4. Interrupted time series analysis and confidence intervals for DMPA users stratified by concurrent combined hormonal contraceptive use

		Combined hormonal contraceptive (yes)				Combined hormonal contraceptive (no)			
Model	Variable	Estimate	LCL	UCL	*p*-value	Estimate	LCL	UCL	*p*-value
(Mean in days)	Intercept	245.6	233.1	258.1	<.0001	204.5	196.1	213.0	<.0001
	Baseline trend	1.3	0.7	1.8	<.0001	1.8	1.5	2.2	<.0001
	Level change	−18.9	−35.3	−2.5	0.026	−36.5	−47.6	−25.5	<.0001
	Trend change	−1.6	−2.2	−0.9	<.0001	−2.4	−2.8	−1.9	<.0001

DMPA, depot medroxyprogesterone acetate; LCL, lower confidence interval; UCL, upper confidence interval.
Baseline trend represents the estimated trend for mean monthly duration or proportions before the boxed warning; level change represents the estimated change immediately after the warning, and trend change represents the estimated change in slope (trend) before and after the boxed warning.

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only changes in use >2 years. This trend may be explained by published recommendations from the American Society for Adolescent Medicine.[17] It states that "DMPA duration of use need not be restricted to 2 years in adolescent population." It is possible that the observed increased level change after the boxed warning in the younger patients is reflective of these recommendations. Given the limited sample size for this subcohort and the absence of the full date of birth in the data, future studies will be needed to confirm these trends.

To date, there have been no other studies examining the impact of the boxed warning on the duration of use of DMPA. Our study has the following implications: first, use of DMPA is not declining over time. Similar trends in the rate of new users in both the DMPA and CHC cohorts observed suggest that the initiation of DMPA has not changed. Second, amidst conflicting guidance, some prescribers and patients in the USA have adopted the 2-year time limit for DMPA use. Third, the analysis stratified by birth cohort suggests that not all patients have adopted the 2-year limit. Specifically, the youngest patients deemed to be at a higher risk for bone mineral loss, continue DMPA for longer than 2 years. Future studies would need to confirm these findings and the resulting effect of long-term DMPA use among adolescents.

Our study has several strengths. First, the ITS is the strongest quasi-experimental design to evaluate longitudinal effects of time-delimited interventions.[19] The model allows for estimating in statistical terms the impact of an intervention on an outcome of interest. Second, our study incorporated a control group of CHC users in the design to assure that the observed changes are related to the intervention of interest and not due to other factors associated with drug utilization in the study dataset. Lastly, our analysis was also able to examine DMPA utilization in a diverse population among women of child-bearing age.

Despite an observed association, there are several limitations that warrant discussion. Although the IMS dataset includes data for a sample of the commercially insured from the 50 US states, this study population may not be generalizable to other target populations, including those with other private insurance and Medicaid. Exposure ascertainment may be different for DMPA and CHCs. DMPA exposure ascertainment was based on procedure codes indicating administration of the injection, while we relied on pharmacy claims for CHC exposure ascertainment. The extent and impact of possible exposure misclassification of the CHC definition remain unknown. Our analysis defined units of analysis (mean duration and proportion >2 years) based on complete duration of use. Therefore, we were unable to capture the impact of the boxed warning on prescribing decision during use. Lastly, in our stratified analysis by birth cohort, some women were excluded because of their estimated age being less than 11 years at index date. Future studies with date of birth information should be conducted to confirm the observed findings by birth cohort.

CONCLUSION

Using an ITS design, we observed a modest decline in the monthly mean duration of use and proportion of patients who have episodes of use greater than 730 days for DMPA use immediately after addition of the boxed warning. This change in utilization was not observed among CHC users. In the stratified analysis, we saw declines in the duration of use >2 years in all age groups, except adolescents who continue to use DMPA for longer than 2 years. Future studies would need to confirm these findings and the effect of long-term DMPA use among adolescents.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- The inclusion of the boxed warning in the US prescription labeling in November 2004 resulted in a decline in the duration of use for depot medroxyprogesterone.
- Declines in the duration of use were observed in all age groups, except for adolescents who continue to use depot medroxyprogesterone for longer than 2 years.
- The effect of long-term depot medroxyprogesterone use among adolescents is warranted, since peak bone accretion occurs during adolescence.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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