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Original Reports

Impact of Sequential Opioid Dose Reduction Interventions in a State Medicaid Program Between 2002 and 2017

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Abstract: **Policies that address opioid dose limits may help to decrease high-risk opioid prescribing. We evaluated 3 sequential and progressive decreases in high-dose (HD) opioid limits implemented by Massachusetts Medicaid over 15 years. The study population included members ages 18 to 64 years with ≥1 claim for a schedule II opioid between January 2002 and March 2017. The 3 interventions consisted of prior authorization requirements for prescriptions exceeding the morphine equivalent dose (MED) HD dose limits: >360 mg (intervention 1a and 1b), >240 mg (intervention 2), and >120 mg (intervention 3). A segmented regression evaluated the change in natural log of the average daily MED (AD_MED). The natural log of the AD_MED decreased during the 6 quarters after intervention 1a ($P < .001$), immediately after intervention 1b ($P = .0002$), and continued to decrease over the following 8 quarters ($P = .023$). The natural log of the AD_MED decreased immediately after intervention 2 ($P = .002$) and again after intervention 3 ($P < .001$). The percentage of users exceeding the HD limits of 360 mg, 240 mg, and 120 mg MED decreased by 87.3%, 79.8%, and 75.2% from baseline, respectively. The natural log of the AD_MED decreased among members after implementation of 3 sequential and progressive HD prior authorization limits, as did the percentage of members exceeding each of the HD limits.**

Perspective: ***This study demonstrates the longitudinal impact of a prior authorization policy-based HD limit in a Medicaid population. This study contributes to options for policymakers and other Medicaid programs as a potential strategy to assist in addressing the opioid epidemic.***

Key words: *Opioid, morphine equivalent dose, high dose, prior authorization, Medicaid, epidemic, policy.*

Opioid misuse and overdose deaths continue to be a serious public health crisis in the United States and prescription opioids have significantly contributed to these deaths.[3] A significant increase in prescription opioids correlates with a 15-year increase in overdose deaths.[18] The overall national opioid prescribing rate steadily increased from 2006 with a peak in 2012 of 255 million in the number of prescriptions dispensed and a rate of 81.3 prescriptions per 100 persons.[4] A 2015 National Survey on Drug Use and Health showed that more than one-third of U.S. civilian noninstitutionalized adults report prescription opioid use.[10] Furthermore, a systematic review of opioid use found a 21 to 29% rate of prescribed opioid misuse with an 8 to 12% addiction rate.[23] These findings emphasize the need for focused, evidence-based treatment guidelines and the need to decrease opioid prescribing that may lead to misuse.

The opioid epidemic has disproportionally affected the Medicaid population, which nationally has a total enrollment of >72 million.[5,16] Compared with non-

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Medicaid beneficiaries, Medicaid beneficiaries are twice as likely to be prescribed an opioid pain medication, with a corresponding overdose risk that is 6 times higher.[6,24] A study of Medicaid beneficiaries showed that 50% of prescribed doses were for >90 morphine equivalent dose (MED) and for periods of >6 months.[22] Medicaid members also suffer from addiction and substance use disorder at a rate 10 times higher than the commercially insured population.[6,25] A 2014 report commissioned by the National Association of Medicaid Directors outlined proposed strategies for states to address prescription drug abuse and overdose, such as retrospective reviews to identify the potential overuse of prescription opioids.[19]

In Massachusetts, the Medicaid pharmacy program implements a number of strategies to reduce use of long-acting opioid analgesics and address issues of high doses. A study compared opioid use from 2002 to 2005 after the implementation of a multifaceted approach that included oversight regarding polypharmacy, dose limits, and duplicate therapy.[8,14] The intervention demonstrated a decreasing trend in the use of long-acting opioid analgesics, a decrease in the quantity of opioids used by each member, and a decrease in the cost to the Medicaid program. The study results were consistent with a 17.8% decrease in long-acting opioid analgesic users and a 4.1% decrease in opioid claims during the study period.[8]

This study aims to evaluate the effect on opioid use of a longitudinal approach focused on 3 sequential and progressive opioid dose reduction interventions through prior authorization (PA) in the MassHealth population from 2002 to 2017. The study focuses on the impact of high-dose (HD) limits on the average daily MED (AD_MED) and percentage of members receiving HD regimens among those receiving schedule II opioids.

Methods

Study Design and Data Source

This study used deidentified enrollment and pharmacy claims data from the MassHealth pharmacy claims processing system. The study was deemed not to be human subject research by the University of Massachusetts Medical School Institutional Review Board and was exempt from review.

Participants

MassHealth members receive services through managed care organizations, fee-for-service plans, and most recently (as of March 2018), accountable care organizations. Participants in this study included those enrolled in the MassHealth Primary Care Clinician plan (internally managed care organizations) and fee-for-service ages 18 to 64 years who had ≥1 schedule II opioid pharmacy claim between January 2002 and March 2017 (Appendix 1).

Opioid formulations combined with acetaminophen or ibuprofen (ie, combination products), meperidine, tapentadol, and intravenous and rectal preparations were excluded. Combination products were excluded owing to the reclassification of hydrocodone-containing products from schedule III to schedule II in October 2014, because they would not have been included in the AD_MED calculation throughout the entirety of the study period. Meperidine, tapentadol, and intravenous and rectal preparations were excluded owing to the very low use of these products. All claims were included regardless of the duration of coverage eligibility, diagnoses (inclusive of cancer), daily ,supply or dose of medication. It should be noted the PA policy allows for medical exception for certain criteria; for example, if a member is in hospice care (under the care of a specialist, meets medical necessity for HD, and patient prescriber agreements are not necessary) or in a long-term care facility (where specialists may not be available for consult and patient prescriber agreements are not necessary). Excluded from the study were MassHealth dual Medicare–Medicaid eligible members and those with other primary prescription insurance coverage. This exclusion was applied to avoid confounding variables that could be introduced based on different PA criteria. Also excluded from the data were MassHealth members receiving methadone through an opioid treatment program for the purposes of treating opioid use disorder, because these regimens are not paid for under the pharmacy benefit of MassHealth and are exempt from the HD limits.

Interventions

We examined the effect of 3 sequential and progressive opioid HD limit interventions on the AD_MED for members receiving ≥1 opioid claim between January 2002 and March 2017. A multidisciplinary therapeutic class management workgroup used a multistep process to define the clinical criteria for the PA process and HD limits. Intervention 1 occurred in 2 phases: 1a and 1b. Intervention 1a was implemented in April 2003 and required prospective PA for a fentanyl patch and oxycodone controlled release prescriptions exceeding the HD limit of 360 mg MED. Intervention 1b was implemented in October 2004 and expanded the PA requirement to morphine, methadone, meperidine, hydromorphone, levorphanol, and oxymorphone prescriptions. In April 2014, intervention 2 was implemented, which required PA for any opioid prescription exceeding the HD limit of 240 mg MED. Finally, intervention 3 was implemented in March 2016, which further decreased the HD limit to 120 mg MED for all opioid prescriptions. The PA process is outlined in Fig 1.

Measures

Demographic characteristics included gender, and age distribution (categorized as 18–24, 25–34, 35–44, 45–54, and 55–64 years). We report the number of members with any opioid use in the population of opioid users by quarter where opioid use was defined as ≥1 prescription in a quarter and the denominator consisted of the entire MassHealth Primary Care Clinician and fee-for-service population. Days' supply was defined as days covered by opioids and counted from the start date to

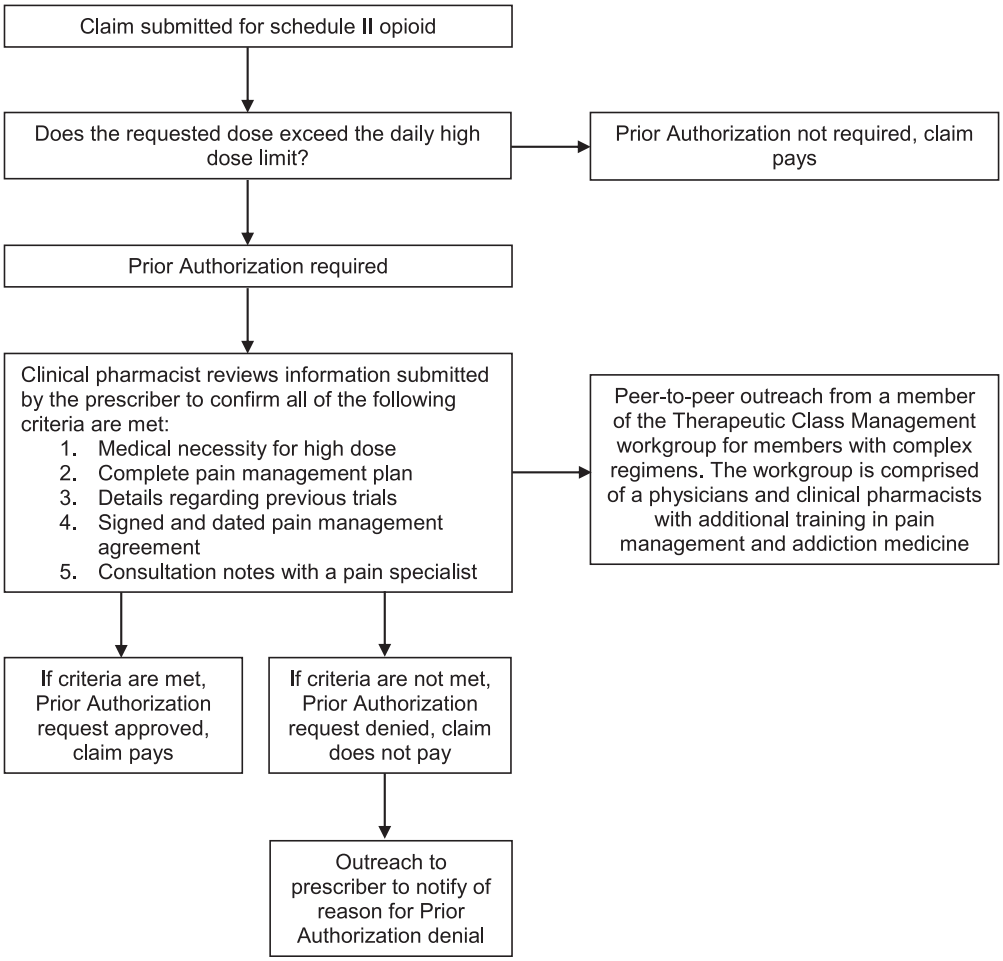

Figure 1. MassHealth HD opioid PA process.

end date of the claim. For each claim, the start date was the date dispensed and the end date was the date dispensed plus the number of the days' supply minus 1. For nonoverlapping prescriptions, total days' supply was calculated as the sum of the days' supply across all prescriptions. For overlapping prescriptions, the days' supply was counted only once. The AD_MED was calculated by the number of pills (or patches) dispensed multiplied by the drug strength, divided by the days' supply, and multiplied by a morphine conversion factor available from the Centers for Disease Control and Prevention's (CDC) National Center for Injury Prevention and Control.[2] For patients with >1 medication available on the same day, the total daily dose was calculated by adding the daily doses for each medication. The daily dose per member per quarter was the sum of the daily doses for each day in the quarter divided by the number of days in the quarter covered by opioid prescriptions. AD_MED dose was broken down by percentiles (50th, 90th, 95th, and 99th) per calendar quarter. We further report the percentage of members receiving HD opioid therapy regimens per quarter using intervention specific HD opioid limits as defined: 1a and 1b (April 2003 and October 2004): >360 mg MED; 2 (April 2014): >240 mg; and 3 (March 2016): >120 mg.

Statistical Analyses

Descriptive statistics were used to characterize the number of schedule II opioid users annually between 2002 and 2017. Because the distribution of average daily doses per quarter was highly skewed, we report median AD_MED dose and interquartile ranges (IQR), along with the 90th, 95th and 99th percentiles. A segmented regression analysis using generalized estimating equations, with autoregressive correlation structure, was performed to estimate the change in members' AD_MED by calendar quarter. Segmented regression fits separate slopes between specified time points, to examine whether the rate of change differs by time segment. We fit the model to estimate the change in quarterly AD_MED during the following segments: 1) 5 calendar quarters before intervention 1a (January 2002 to March 2003); 2) intervention 1a to intervention 1b (April 2003 to September 2004); 3) 6 quarters after intervention 1b (October 2004 to March 2005); 4) 6 quarters before intervention 2 (October 2013 to March 2014); 5) intervention 2 to intervention 3 (April 2014 to March 2016); and 6) 4 calendar quarters after intervention 3 (April 2016 to March 2017). We used the natural log of the average daily dose as the outcome variable to account for the skewed distribution of AD_MED. Models

controlled for demographic characteristics of the study population. Because the length of time between interventions 1b and 2 was >10 years, we tested the effect of interventions 1a and 1b (from 6 quarters before intervention 1a through 8 quarters after intervention 1b) in 1 model and interventions 2 and 3 (from 9 quarters before intervention 2 and 5 months after intervention 3) in separate models.

Results

The annual number of opioid users increased from 4.3% of total enrollees in 2002 to 5.4% in 2015 with a peak of 8.0% in 2013 (Table 1). In each year of the study period, there was a higher percentage of female opioid users compared with males. The percentage of opioid users ages 18 to 24 was 5.8% in 2002, whereas in 2016, 9.7% of opioid users were ages 18 to 24. The same trend was seen for members ages 55 to 64 who represented 16.1% of the opioid users in 2002 and 25.6%of users in 2016. In 2002, members ages 35 to 44 represented the group with the highest opioid use (32.2%), whereas in 2016, members ages 45 to 54 represented the highest percentage of use (25.7%).

During the first quarter of the study period (January to March 2002) the AD_ MED was 90 mg (IQR = 60−180 mg; Fig 2A). The median AD_MED peaked in the eighth quarter of the study period (October to December 2003) at 113 mg (IQR = 60−210 mg). In the final quarter of the study period (January to March 2017), the median AD_MED was 50 mg (IQR = 30−88 mg), a decrease of 55.8% from the peak of 113 mg. The greatest relative change in AD_MED was noted among doses in the 99th percentile. Although 1% of members had a mean AD_MED of ≥1,218 mg in January to March 2003, this decreased to 360 mg in January to March 2017, a decrease of 70.4% (Fig 2B). Fig 2A presents the mean and median AD_MED and Fig 2B presents the 90th, 95th, and 99th percentiles of the AD_MED over the study period.

The natural log of the AD_MED among members prescribed opioids increased slightly during the 6 calendar quarters before intervention 1a ($P < .001$) and began to decrease during the 6 quarters after the intervention ($P < .001$). The natural log of the AD_MED decreased again immediately after intervention 1b ($P = .0002$) and continued to decrease over the following 8 quarters ($P = .023$). Although the natural log of the AD_MED did not change during the 9 quarters before intervention 2, it decreased immediately after intervention 2 ($P = .002$) and again after intervention 3 ($P < .001$), but remained steady during the subsequent 4 quarters (the full model estimates in are provided in Appendix 2).

The percentage of members exceeding the average daily HD limit of 360 mg MED was 7.7% at the beginning of the study period and continued to increase for 3 quarters to a peak of 9.1% in October to December 2003 (Fig 3). It then decreased throughout most of the remainder of the study period, ending at .97% in January to March 2017 (an 87.3% reduction from the

Table 1. Demographic Characteristics of Members Prescribed Schedule II Opioids, Annually, January, 2002 to March, 2017

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017 (JAN–MAR)
Total enrollees	266,379	227,295	238,129	250,090	258,372	261,643	271,952	283,449	287,157	283,821	294,102	276,261	402,827	314,037	340,072	360,376
Total unique opioid users	11,465	11,403	11,790	12,785	13,630	14,462	15,641	15,810	20,042	20,016	22,012	22,057	25,005	22,097	18,456	8,003
Percentage of opioid users in population	4.3	4.1	5.0	5.1	5.3	5.5	5.7	5.6	7.0	7.1	7.5	8.0	6.2	7.0	5.4	2.2
Demographic characteristics, n (%)																
Male	5,024 (43.8)	4,947 (43.4)	5,207 (44.2)	5,705 (44.6)	6,100 (44.8)	6,645 (45.9)	7,281 (46.6)	7,692 (48.7)	9,936 (49.6)	9,656 (48.2)	10,558 (48)	10,385 (47.1)	10,882 (43.5)	8,766 (39.7)	7,238 (39.2)	3,118 (39)
Female	6,441 (56.2)	6,456 (56.6)	6,583 (55.8)	7,080 (55.4)	7,530 (55.2)	7,817 (54.1)	8,360 (53.4)	8,118 (51.3)	10,106 (50.4)	10,360 (51.8)	11,454 (52)	11,672 (52.9)	14,123 (56.5)	13,331 (60.3)	11,218 (60.8)	4,885 (61)
Ages 18–24	669 (5.8)	614 (5.4)	675 (5.7)	744 (5.8)	880 (6.5)	1,044 (7.2)	1,226 (7.8)	1,190 (7.5)	1,871 (9.3)	1,708 (8.5)	1,847 (8.4)	1,807 (8.2)	2,212 (8.8)	2,109 (9.5)	1,798 (9.7)	541 (6.8)
Ages 25–34	2,018 (17.6)	1,836 (16.1)	1,871 (15.9)	1,955 (15.3)	2,019 (14.8)	2,276 (15.7)	2,544 (16.3)	2,707 (17.1)	3,840 (19.2)	3,826 (19.1)	4,414 (20.1)	4,305 (19.5)	4,994 (20)	4,366 (19.8)	3,474 (18.8)	1,198 (15)
Ages 35–44	3,692 (32.2)	3,575 (31.4)	3,516 (29.8)	3,583 (28)	3,737 (27.4)	3,691 (25.5)	3,920 (25.1)	3,737 (23.6)	4,532 (22.6)	4,430 (22.1)	4,851 (22)	4,704 (21.3)	5,093 (20.4)	4,558 (20.6)	3,729 (20.2)	1,465 (18.3)
Ages 45–54	3,238 (28.2)	3,358 (29.4)	3,566 (30.2)	4,058 (31.7)	4,454 (32.7)	4,663 (32.2)	4,985 (31.9)	5,008 (31.7)	5,999 (29.9)	6,127 (30.6)	6,465 (29.4)	6,508 (29.5)	6,884 (27.5)	5,735 (26)	4,734 (25.7)	2,264 (28.3)
Ages 55-64	1,848 (16.1)	2,020 (17.7)	2,162 (18.3)	2,445 (19.1)	2,540 (18.6)	2,,788 (19.3)	2,966 (19)	3,168 (20)	3,800 (19)	3,925 (19.6)	4,435 (20.1)	4,733 (21.5)	5,822 (23.3)	5,329 (24.1)	4,721 (25.6)	2,535 (31.7)

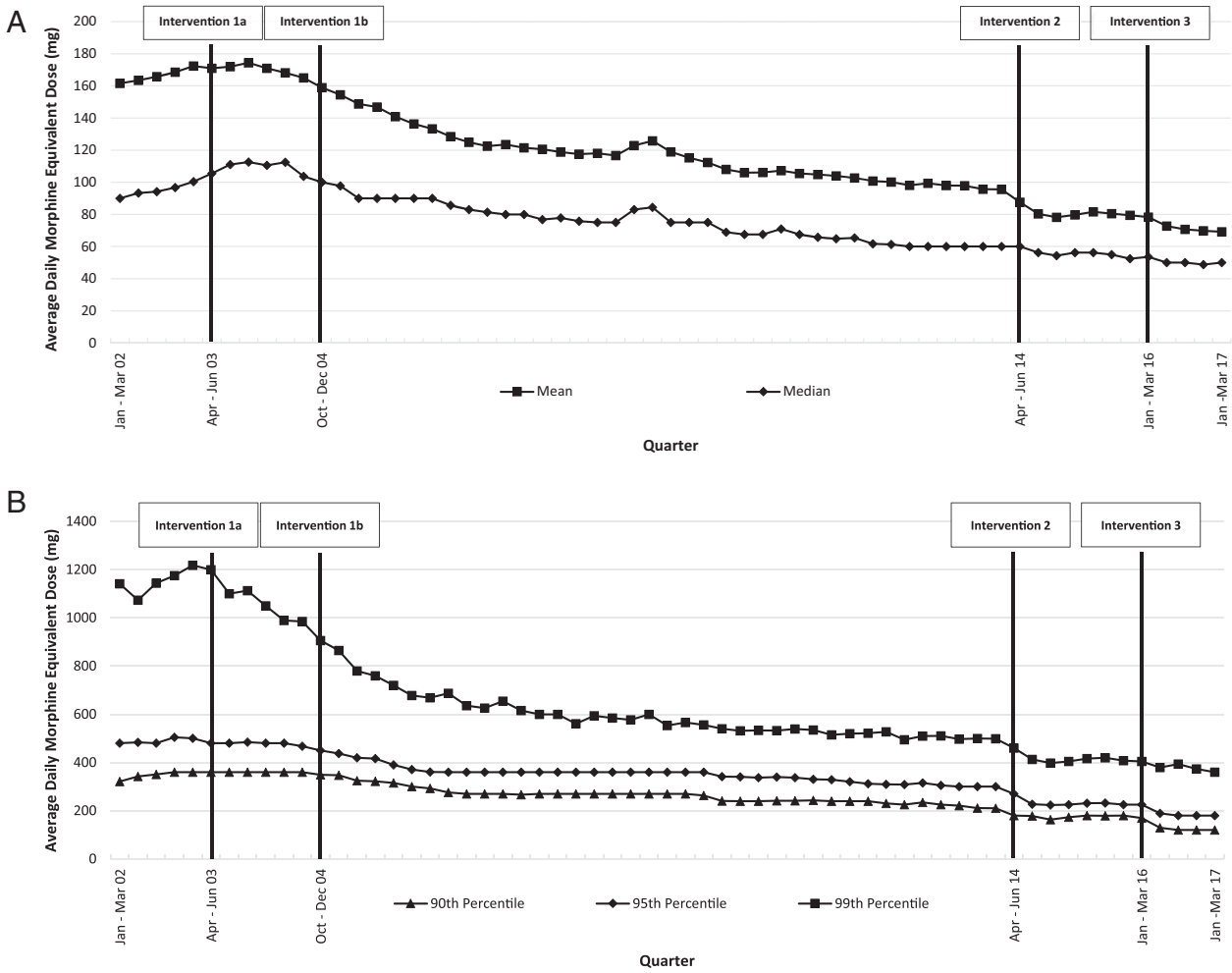

Figure 2. (A). Mean and median AD_MED among members prescribed schedule II opioids, before and after the intervention by calendar quarters, January to March 2002 through January to March 2017. Intervention 1a (April 2003): PA required for fentanyl patch and oxycodone controlled release prescriptions exceeding the HD limit of 360 mg MED. **(B)** The 90th, 95th, and 99th percentiles of AD_MED among members prescribed schedule II opioids, before and after the intervention by calendar quarters, January to March 2002 through January to March 2017. Intervention 1b (October 2004): PA requirement expanded to also include morphine, methadone, meperidine, hydromorphone, levorphanol, and oxymorphone prescriptions exceeding the HD limit of 360 mg MED.

beginning of the study period). This trajectory is similar when the HD threshold is set at 240 mg and 120 mg. From the beginning to the end of the study period, there was a decrease of 79.8% and 75.2% in the percentage of members exceeding an AD_MED of 240 mg (from 15.2% to 2.5%) and 120 mg (from 36.0% to 8.9%), respectively.

Discussion

Since the 1990s, there has been a high supply of prescription opioids in the United States.[17] This increase in prescription opioids has driven state policymakers to reduce inappropriate opioid prescribing rates. It is in our collective interest as health care providers to ensure that patients are appropriately treated for pain; however, all prescribers and payers must balance this factor with monitoring for continued medical necessity, risk of abuse, and addiction. The MassHealth PA strategy attempts to strike the balance of providing appropriate pain management that includes opioid treatment with guidelines that minimize the risk of chronic and HD use. Our study found that a sequential and progressive opioid dose reduction strategy was successful in decreasing the average daily opioid dose among a population of Medicaid members in 1 state. This study is among the first to show the impact of a mandatory PA policy-based HD limit in this population.

We observed a number of opioid use trends in our state's Medicaid population that are consistent with national trends. Since 2002, users of schedule II opioids in our population increased by 46.3% to a peak in 2013, from 4.3% to 8.0% of the total population. In 2016, members ages 45 to 54 and 55 to 64 years represented the highest proportion of users. With the exception of the 3 quarters between October and December 2008 and April and June 2009, the impact of each HD opioid intervention was maintained over time as defined by AD_MED and percentage of users above each HD threshold. Our data also show a decrease since 2002 in the percentage of members ages 35 to 44 years using opioids, while the percentage of those ages 55 to

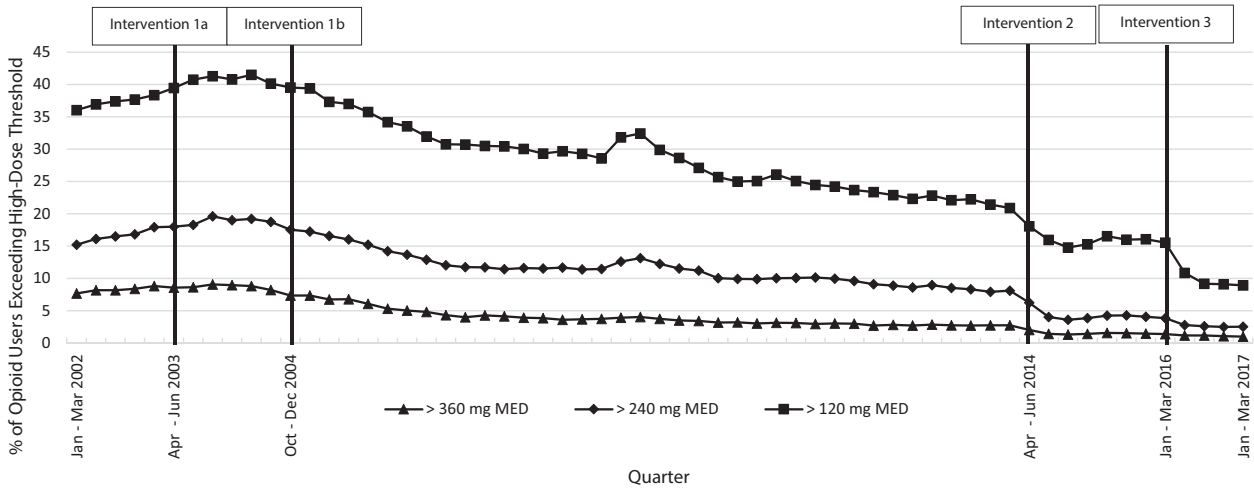

Figure 3. Percentage of members exceeding morphine equivalent HD limits among those prescribed schedule II opioids, by calendar quarters, January to March 2002 through January to March 2017. Intervention 2 (April 2014): PA required for all opioid prescriptions exceeding the HD limit of 240 mg MED. Intervention 3 (March 2016): PA required for all opioid prescriptions exceeding the HD limit of 120 mg MED.

64 years using opioids increased by 37% between 2002 and 2016. This finding is a concern, because an older population may be burdened with more disabilities and comorbidities and therefore at greater risk of opioid-related adverse events.[15] The age group with the greatest increase in opioid use in our data (ages 55–64) is the same age group that the CDC reports as having greatest increase in overdose death rates.[12] Our data also identified women as the higher users of opioids, which is consistent with CDC data reporting that deaths from opioid pain relievers increased 5-fold for women between 1999 and 2010 compared with an increase of 3.6 times among men.[21]

PA is 1 tool that Medicaid programs can apply to control the use of a medication with clinical, safety, or economic intent. Although a number of PA strategies have been implemented to address inappropriate opioid use, few have evaluated their impact on high-risk use or member outcomes. An evaluation of a PA policy for extended release and long-acting opioids was conducted among fee-for-service Medicaid members in Oklahoma. Compared with a control group without a similar PA policy in place (Oregon Medicaid), incident use of extended-release or long-acting opioids decreased while the use of short-acting agents increased. There was no significant difference observed in emergency department use or hospitalizations among the groups.[13] Similar to our study, a recent analysis of Oregon Medicaid revealed that after implementation of an HD limit (120 mg MED), the number of fills for dosages above the limit decreased by 1.7% and, among members with HD fills before the policy, there was a 20.3% decrease in the estimated probability of having a postpolicy HD fill. No differences in opioid overdose were observed.[11] These analyses underline the importance of policy evaluation to understand whether the intent is being met and if there are unintended consequences that should be addressed.

The results of our study are consistent with studies that evaluated the impact of an opioid dosing guideline developed by the Washington State Agency Medical Directors' Group.[1] Garg et al[9] reported the impact of this guideline implementation among workman's compensation patients between 2004 and 2010. Although the median daily opioid dose remained stable during the study period, users were 34.9% less likely to receive doses of ≥120 mg MED per day after implementation of the guideline. A decrease was also observed in the prevalence of the mean number of monthly opioid users. However, the extent to which these changes were due to the guideline cannot be established because it was not accompanied by policy enforcement and the study was not designed to control for other impacting factors. In 2015, Sullivan et al[20] evaluated opioid prescribing among Washington State Medicaid adults after implementation of the aforementioned guideline and found that the median opioid dose remained unchanged between 2006 and 2010, but that doses at the higher percentiles decreased significantly. The authors suggested that treatment guidelines may be able to decrease HD opioid use without affecting the median dose used. Our results are similar to those seen in Washington state, with the greatest decreases observed among doses at the highest percentiles. However, comparisons should be made with caution because our study evaluated a mandatory intervention (ie, the HD limit was implemented through PA policy), included only schedule II opioid medications, and included any Medicaid member who received an eligible claim regardless of their underlying diagnosis.

A notable component of MassHealth's opioid initiative is that it does not exclude members based on diagnosis. In other words, even if a member has a cancer diagnosis, clinical criteria establishing medical necessity and HD must be met, rather than this member being

automatically excluded from the initiative and bypassing the safety measures applied through the PA policy. In most circumstances, when a member has cancer, HD opioid PAs are approved because the criteria for medical necessity and specialist review are met. Although a number of payer programs exclude members with cancer from opioid-related PA policies, we do not apply automatic exclusions owing to limitations of the billing system and the risk for missing members who would otherwise benefit from the opioid initiative. For example, there is a time lag for medical coding to be integrated into the medical claims system and subsequently into the pharmacy claims system. This factor would therefore limit the system's ability to identify members who are newly diagnosed with cancer. In addition, a diagnosis code may stay attached to the member profile for a prolonged period of time. This factor limits the system's ability to detect members whose cancer is in remission and would possibly no longer medically need opioids or escalating doses.

Increased awareness and regulatory efforts around opioid misuse across the country, as well as in Massachusetts, may have contributed to the decreasing trends observed among our population. At the national level, there was the introduction of abuse deterrent opioid formulations. We also saw the development of systematic educational efforts, the CDC opioid prescribing guideline,[7] and the use of prescription drug management programs. Specific to Massachusetts, in March 2016 (the same month as intervention 3), legislation was enacted that limited the days' supply of initial opioid prescriptions. We do not think it is likely that this legislation impacted our results because it only targets the duration of a new-start opioid prescription rather than the dose. Although external initiatives are likely to have impacted opioid use during this study period, the interrupted time series approach provides evidence that the AD_MED decreased after the HD limit opioid interventions. Overall, we demonstrated that the impact of each intervention was sustained over time. To ensure success of the policy, we developed each step with consideration of the potential impact on prescribers and members in a conscientious, stepwise, and evidence-based approach to dosing limits (rather than quantity) to avoid introduction of abrupt changes.

Limitations of this analysis should be noted. This study only included schedule II opioids and excluded opioid combination products, which overall are the most commonly used opioid formulations in our population; however, as noted in the Introduction, owing to the reclassification of hydrocodone-containing products, the AD_MED calculation would have been confounded and not been an accurate reflection throughout the study period. In addition to hydrocodone-containing products, other combination products were excluded because the HD limits evaluated in this study are not generally achieved by these medications owing to limits on acetaminophen and ibuprofen. Another limitation is that these data represent a subgroup of one state's Medicaid members; however, it should be noted that, in total, MassHealth covers roughly 1.86 million members or approximately 28% of the Massachusetts population. Our dataset does not include prescriptions paid with cash because we did not have access to the prescription drug monitoring program owing to state regulation. Therefore, the calculated AD_MED may be lower than that based on actual use. Furthermore, we did not evaluate opioid overdose rates or health care use (ie, hospitalization and emergency room use) or evaluate outcomes according to member demographics (age and gender), which limits the generalizability of results. Finally, the interrupted time series approach is limited in controlling for concurrent events at the national and state levels.

Conclusions

Our study found that a sequential and progressive opioid dose reduction strategy was successful in decreasing the average daily opioid dose among Medicaid members in Massachusetts. It also showed a significant decrease in members receiving the highest doses. We feel that this study contributes options for policymakers and other Medicaid programs to consider as potential strategies to assist in addressing the opioid epidemic.

Acknowledgments

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Appendix 1. List of included schedule II opioids (note: opioid formulations in combination with acetaminophen or ibuprofen, combination products such as hydrocodone-containing products that changed to Schedule II in October 2014, products containing acetaminophen, meperidine hydrochloride, tapentadol and intravenous and oral preparations were excluded).

Codeine phosphate
Codeine sulfate
Fentanyl
Hydrocodone bitartrate
Hydromorphone hydrochloride
Levorphanol tartrate
Methadone hydrochloride
Morphine sulfate
Morphine sulfate/naltrexone
Oxycodone hydrochloride
Oxymorphone hydrochloride

Appendix 2. General Estimating Equation Model Parameters

	Beta	*95% Confidence Interval*	P *Value*	*Percent Change in Median AD_MED**	*95% Confidence Interval*
Intercept	4.1				
Quarter	.027	.019 to .034	<.001	2.74	1.92 to 3.46
Intervention 1a	−.006	−.022 to .011	.489	−.60	−2.18 to 1.11
Time after intervention 1a	−.02	−.03 to .011	<.001	−1.98	−2.96 to −1.09
Intervention 1b	−.03	−.045 to .014	.0002	−2.96	−4.4 to −1.39
Time after intervention 1b	−.009	−.069 to −.001	.023	−.90	−6.67 to −.1
Intercept	4.076				
Quarter	−.002	−.006 to .001	.1872	−.20	−.6 to .1
Intervention 3	−.027	−.042 to −.013	.0002	−2.66	−4.11 to −1.29
Time after intervention 3	−.003	−.009 to .002	.2342	−.30	−.9 to .2
Intervention 4	−.031	−.045 to −.016	<.0001	−3.05	−4.4 to −1.59
Time after intervention 4	−.006	−.014 to .002	.1238	−.60	−1.39 to .2

*(EXP(beta)-1)*100.

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