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The role of unit-dose child-resistant packaging in unintentional childhood exposures to buprenorphine-naloxone tablets

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Dear Editor,

Buprenorphine-naloxone was among the most commonly implicated exposures in pediatric emergency department (ED) visits for unsupervised oral prescription medication ingestions in 2007-2011, resulting in high hospitalization rates [1, 2] and several deaths.[3]

Buprenorphine-naloxone products are available as sublingual tablets and, since 08/2010, as sublingual film dispensed in child-resistant unit-dose packaging (UDP). Buprenorphine-naloxone tablets are dispensed in multidose bottles, and, since 07/2013, also in UDP. Several studies have detected decreasing rates of childhood exposures for buprenorphine-naloxone products since the introduction of the film,[2, 4] and lower rates associated with the film compared to the tablet.[3] However, only one study distinguished between the effects of the dosage form and UDP.[4] Wang et al. detected a statistically significant decline in poison control calls for childhood exposures to buprenorphine-naloxone tablets with increasing UDP use; however, the extent of decline far exceeded the UDP dispensing rate. To further investigate the effects of UDP, we compared ED visit rates for pediatric ingestion of buprenorphine-naloxone tablets prior to the introduction of UDP (2008-2011) with rates after the introduction of UDP (2015-2017), excluding a transition period.

We calculated utilization-adjusted rates of ED visits for buprenorphine-naloxone tablet ingestions by children aged <6 years for 2008–2017 using two national samples: the 60 hospital National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project and the IQVIA National Prescription Audit. NEISS-

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Disclaimer:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of FDA or CDC.

Ethical Approval: This project meets the definition of a public health surveillance activity described in 45 CFR 46.102(1)(2) and does not require human subjects review or IRB approval.

Conflict of Interest: Christian Hampp, Maribeth C Lovegrove, Daniel S Budnitz, Justin Mathew, Amy Ho, and Jana McAninch have no conflicts of interest that are directly relevant to the content of this study.

CADES cases are weighted based on the inverse probability of selection and adjusted for nonresponse and number of ED visits.[1] IQVIA uses a proprietary algorithm to project national estimates of dispensed prescriptions. Using a two-tailed test, we compared prescription-adjusted ED visit rates between 2008-2011 and 2015-2017. We performed six sensitivity analyses with varying rules for categorizing ED visits involving tablet formulations only.

The estimated annual number of buprenorphine-naloxone dispensings from U.S. outpatient pharmacies increased from 3.18 million in 2008 to 11.0 million in 2017 (Figure 1). During most years, the film was the predominant dosage form. In 2017, tablets accounted for 28.9% of all dispensings. The proportion of tablets dispensed in UDP increased since 2013 and peaked in 2016 (44.6%), followed by a small decline in 2017 (41.9%).

Based on 156 cases, there were an estimated 6,892 (95% CI, 4,134-9,651) ED visits for buprenorphine-naloxone tablet ingestions by children aged <6 years from 2008-2017. Most (58.4%; 48.3-68.5%) ED visits involved children under age 2, 51.4% (95% CI, 39.9-62.9%) involved boys, and 71.0% (95% CI, 55.8-86.2%) resulted in hospitalization.

There were an estimated 26.3 (95% CI, 15.5-37.0) ED visits for pediatric ingestions per 100,000 buprenorphine-naloxone tablet dispensings annually during 2008-2011. The ED visit rate declined by 27.7% ($p=0.35$) to 19.0 (95% CI, 7.7-30.3) per 100,000 dispensings annually during 2015-2017 (Figure 2), while the proportion of tablets dispensed in UDP increased from 0% to 37.6%. The relative decline in ED visits ranged from 12.6% to 34.0% across six sensitivity analyses.

Most buprenorphine-naloxone tablets continue to be dispensed in multi-dose bottles, which limited power to detect significant change in ED visit rates. Although the finding of a 27.7% decrease in ED visit rates with 37.6% UDP penetration is consistent with a protective effect, statistical uncertainty precludes conclusive determination. Beside random error, longitudinal trends in ED visits overall and campaigns advocating for safe use and storage may also have contributed.

We encourage the use of UDP for buprenorphine-naloxone products, particularly for households with young children. Child-resistant UDP obviates the need for adults to re-secure bottle caps. This passive protection should limit unintentional ingestions by children, [5, 6] and, if breached, limit the amount available for ingestion. With continued use of UDP and monitoring of ingestions, conclusive determination of impact should become possible.

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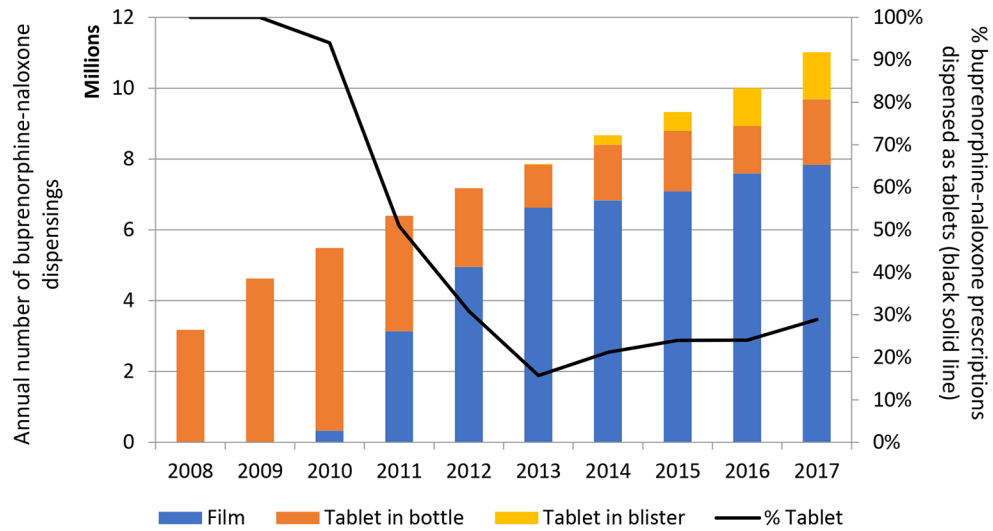


Figure 1. Nationally projected number of prescriptions dispensed for buprenorphine-naloxone oral products from U.S. retail pharmacies, stratified by dosage form and type of tablet packaging, 2008-2017.

Nationally projected prescription data from 2008-2017 were extracted from the IQVIA: National Prescription Audit (NPA). IQVIA NPA contains de-identified prescription level data from U.S. retail pharmacies representing 92% of the prescriptions dispensed nationally. These data are then projected to represent 100% of prescription drugs filled at retail pharmacies. Key dates include: Suboxone buprenorphine-naloxone film available in unit-dose packaging available (August 2010); first buprenorphine-naloxone tablets (Zubsolv) available in unit-dose blister packaging (July 2013).

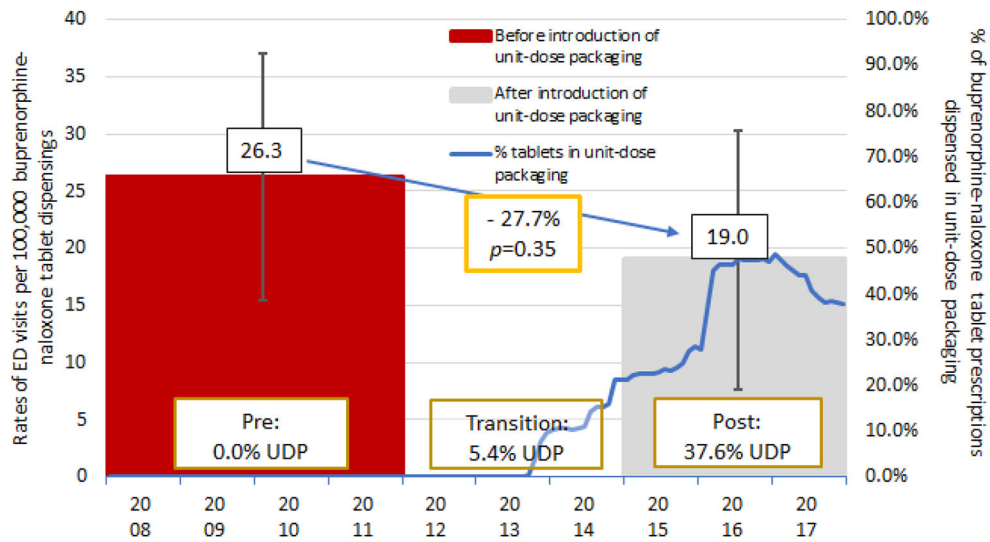


Figure 2. Nationally projected rates of emergency department visits for unsupervised buprenorphine-naloxone tablet ingestions by children aged <6 years per 100,000 dispensed buprenorphine-naloxone tablet prescriptions, compared with proportions of tablet prescriptions dispensed in unit-dose packaging, United States, 2008-2017
 Estimates of ED visits for pediatric (age <6) buprenorphine-naloxone ingestions were based on 2008–2017 data from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project. Estimates of the percentage of buprenorphine-naloxone tablets dispensed in unit-dose packaging were based on data from the IQVIA: National Prescription Audit.