

ENFORCEMENT AND COMPOUNDING COMMITTEE REPORT

Amy Gutierrez, PharmD, Chair, Board President

Greg Lippe, Public Member, Vice Chair

Stan Weisser, Professional Member

Allan Schaad, Professional Member

Rosalyn Hackworth, Public Member

Greg Murphy, Public Member

I. NEW ITEMS

a. Centers for Disease Control and Prevention's Draft Guidelines for Prescribing Opioids for Chronic Pain, Including Staff's Letter of Support

On December 14, 2015, the Centers for Disease Control and Prevention published its Proposed 2016 Guideline for Prescribing Opioids for Chronic Pain. A copy of the draft guidelines as well as the board's letter of support is provided in **Attachment A**.

The following is the Report of the Enforcement and Compounding Committee (committee) meeting held on December 14, 2015.

II. ENFORCEMENT MATTERS

a. Report on the Presentation by the California Department of Health Care Services on California's Drug Utilization Review Program and the Medi-Cal DUR Educational Bulletin on "Morphine Equivalent Daily Dose to Prevent Opioid Overdose"

Recent studies demonstrate that a patient's cumulative Morphine Equivalent Daily Dose (MEDD) is an indicator of potential dose-related risk for adverse drug reactions to opioids, including overdose. As a result, many state Medicaid Drug Utilization Review (DUR) programs have established recommendations for MEDD or opioid dose limitation.

There is housed in the California Department of Health Care Services a DUR Committee that supports the state's Medi-Cal program in creating drug benefits. Board Member Allen Schaad asked that this program provide an overview of its duties and functions to the board's Enforcement and Compounding Committee. There were two presentations as part of this segment:

- Pauline Chan, R.Ph., MBA, California Department of Health Care Services

- Shal Lynch, PharmD, CGP, Health Sciences Associate Clinical Professor
UCSF Department of Clinical Pharmacy, School of Pharmacy

At the committee meeting

Ms. Chan provided an overview of the Medi-Cal DUR program, and discussed the Medi-Cal DUR educational bulletin “Morphine Equivalent Daily Dose to Prevent Opioid Overdose.” The committee also heard information from Ms. Lynch regarding the evaluation of MEDD in patient care.

A copy of the article as well as a copy of the presentations is provided in **Attachment 1**.

There were no public comments.

Committee Recommendation:

Add the MEDD educational bulletin to the board’s website.

b. Legislative Proposal for the Board of Pharmacy to Establish a List of Synthetic Cannabinoids that Would be Illegal for Use in California

Spice (synthetic cannabinoids) and *bath salts* (synthetic cathinones) refer to two groups of designer drugs that have increased in popularity in recent years. These substances are created with *analogs* of commonly used illicit drugs. An analog is one of a group of chemical compounds that are similar in structure and pharmacology. **Attachment 2** contains a number of fact sheets on these products.

A form of synthetic cannabinoids, commonly referred to as “Spice” or “K2,” is designed to affect the body in a manner similar to marijuana, but is not derived from the marijuana plant. These substances began appearing across the U.S. in 2008, and their popularity grew over the following years mainly because they could be sold legally and not detected in urinalysis drug tests.

Synthetic cannabinoids are not currently identified using routine screening tests, and the creation of new products of this type makes it difficult to detect these chemicals or regulate products that contain these substances.

Although these substances were made illegal nationally in 2012, synthetic cannabinoids and cathinones remain available, generally through black market internet sites, indicating a need for continued education, prevention, and enforcement.

California’s Health and Safety Code as amended effective January 1, 2016 provides the following:

11375.5. [Stimulants]

- (a) Every person who sells, dispenses, distributes, furnishes, administers, or gives, or offers to sell, dispense, distribute, furnish, administer, or give, any synthetic stimulant compound specified in subdivision (c), or any synthetic stimulant derivative, to any person, or who possesses that compound or derivative for sale, is guilty of a misdemeanor, punishable by imprisonment in a county jail not to exceed six months, or by a fine not to exceed one thousand dollars (\$1,000), or by both that fine and imprisonment.
- (b) Every person who uses or possesses any synthetic stimulant compound specified in subdivision (c), or any synthetic stimulant derivative, is guilty of *an infraction, punishable by a fine not to exceed two hundred fifty dollars (\$250)*.
- (c) Unless specifically excepted, or contained within a pharmaceutical product approved by the United States Food and Drug Administration, or unless listed in another schedule, subdivisions (a) and (b) apply to any material, compound, mixture, or preparation which contains any quantity of a substance, including its salts, isomers, esters, or ethers, and salts of isomers, esters, or ethers whenever the existence of such salts, isomers, esters, or ethers, and salts of isomers, esters, or ethers is possible, that is structurally derived from 2-amino-1-phenyl-1-propanone by modification in one of the following ways:
 - (1) By substitution in the phenyl ring to any extent with alkyl, alkoxy, alkylenedioxy, haloalkyl, or halide substituents, whether or not further substituted in the phenyl ring by one or more other univalent substituents.
 - (2) By substitution at the 3-position with an alkyl substituent.
 - (3) By substitution at the nitrogen atom with alkyl or dialkyl groups, or by inclusion of the nitrogen atom in a cyclic structure.
- (d) This section shall not prohibit prosecution under any other provision of law.

And

11357.5. [Synthetic Cannabinoids]

- (a) Every person who sells, dispenses, distributes, furnishes, administers, or gives, or offers to sell, dispense, distribute, furnish, administer, or give, or possesses for sale any synthetic cannabinoid compound, or any synthetic cannabinoid derivative, to any person, is guilty of a misdemeanor, punishable by imprisonment in a county jail not to exceed six months, or by a fine not to exceed one thousand dollars (\$1,000), or by both that fine and imprisonment.
- (b) Every person who uses or possesses any synthetic cannabinoid compound, or any synthetic cannabinoid derivative, is guilty of an infraction, punishable by a fine not to exceed two hundred fifty dollars (\$250).
- (c) As used in this section, the term “synthetic cannabinoid compound” refers to any of the following substances:
 - (1) Adamantoylindoles or adamantoylindazoles, which includes adamantyl carboxamide indoles and adamantyl carboxamide indazoles, or any compound structurally derived from 3-(1-adamantoyl)indole, 3-(1-adamantoyl)indazole, 3-(2-adamantoyl)indole, N-(1-adamantyl)-1H-indole-3-carboxamide, or N-(1-adamantyl)-1H-indazole-3-carboxamide

by substitution at the nitrogen atom of the indole or indazole ring with alkyl, haloalkyl, alkenyl, cyanoalkyl, hydroxyalkyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidinyl)methyl, 2-(4-morpholinyl)ethyl, or 1-(N-methyl-2-pyrrolidinyl)methyl, 1-(N-methyl-3-morpholinyl)methyl, or (tetrahydropyran-4-yl)methyl group, whether or not further substituted in the indole or indazole ring to any extent and whether or not substituted in the adamantyl ring to any extent, including, but not limited to, 2NE1, 5F-AKB-48, AB-001, AKB-48, AM-1248, JWH-018 adamantyl carboxamide, STS-135.

- (2) Benzoylindoles, which includes any compound structurally derived from a 3-(benzoyl)indole structure with substitution at the nitrogen atom of the indole ring with alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidinyl)methyl, 2-(4-morpholinyl)ethyl, or 1-(N-methyl-2-pyrrolidinyl)methyl, 1-(N-methyl-3-morpholinyl)methyl, or (tetrahydropyran-4-yl)methyl group, whether or not further substituted in the indole ring to any extent and whether or not substituted in the phenyl ring to any extent, including, but not limited to, AM-630, AM-661, AM-679, AM-694, AM-1241, AM-2233, RCS-4, WIN 48,098 (Pravadoline).
- (3) Cyclohexylphenols, which includes any compound structurally derived from 2-(3-hydroxycyclohexyl)phenol by substitution at the 5-position of the phenolic ring by alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidinyl)methyl, 2-(4-morpholinyl)ethyl, or 1-(N-methyl-2-pyrrolidinyl)methyl, 1-(N-methyl-3-morpholinyl)methyl, or (tetrahydropyran-4-yl)methyl group, whether or not further substituted in the cyclohexyl ring to any extent, including, but not limited to, CP 47,497, CP 55,490, CP 55,940, CP 56,667, cannabicyclohexanol.

And more of this follows in the section.

At the committee meeting

The committee reviewed and discussed a legislative concept that would be authored as 2016 legislation by Senator Hernandez to have the Board of Pharmacy establish a list of synthetic cannabinoids and stimulants that would be illegal for use in California until incorporated formally as statutory modifications into Health and Safety Code sections 11375.5 and 11357.5. Currently the Senator's office is working on the language.

Ms. Herold explained that the Controlled Substances Act is very specific. Because it is so specific about the type of substances that are illegal, one molecule of the substance can be changed to make the substance legal. The process to address the new substance and make it illegal by adding it to statute is long and complicated. Therefore, Senator Hernandez wants to find a way by which the board could provide an interim step, perhaps by emergency, short term regulations. This would allow law enforcement to use the board's regulation to arrest and prosecute vendors while the Department of Justice seeks revisions to the permanent statute.

Committee Recommendation:

Work with Senator Hernandez to develop the legislative concept.

c. Update on the University of California, San Diego’s Pilot Program to Permit Patients to Access Medications from an Automated Storage Device not Immediately Adjacent to a Pharmacy

At the Board of Pharmacy’s April 2015 Board Meeting, the board approved an 18-month pilot study under the auspices of the UCSD School of Pharmacy. The study involves the use of an automated storage device from which staff and the families of a Sharp Hospital in San Diego, who opt in, may pick up their outpatient prescription medications. This device is located in a hospital and should be more convenient for employees than having to go to the community pharmacy. Consultation will be provided via telephone before medication can be dispensed to a patient.

This study was planned to start in June or July, 2015; however, at the September 9, 2015 Enforcement Committee meeting, Dr. Jan Hirsch, BS Pharm, PhD, spoke via telephone and anticipated the pilot study would not begin until December.

At the committee meeting

Dr. Hirsch provided an update via telephone and stated that the study would go live on December 15, 2015. She provided a timetable which indicated that UCSD began a pre-kiosk 6-month data collection during the last quarter of 2015. She stated they would launch the device, enroll patients and refine data collection tools and processes during the first quarter of 2016, collect and review the data during the third quarter of 2016, and report back to the board with their results during the last quarter of 2016.

The committee heard a public comment about whether UCSD would report at a drug-specific level and whether the study would be able to compensate for seasonal fluctuations (e.g., cold/flu season). Dr. Hirsch answered that the study will look at the return to stock rate for the pharmacy vs. the kiosk.

Dr. Gutierrez asked whether the drug class would be included in the data. Dr. Hirsch stated she thought they should have thought about collecting data at the drug class level and would be open to adding that data.

A copy of Dr. Hirsch’s presentation is included in **Attachment 3**.

Committee Recommendation:

Request the collection of drug classifications as part of the study.

d. Sunset Review Proposals

The board's 2016 Sunset Report was submitted to the Legislature when it was due on December 1, 2015. Below are several issues highlighted in the report.

1. Regulation of Outsourcing Facilities by the Board

In 2012, medication contaminated by fungal material that was compounded by a Massachusetts pharmacy killed 65 and injured approximately 700 individuals in various states. In response, the California Board of Pharmacy initiated a review of its then sterile injectable compounding requirements that had been enacted in 2001. Among other actions, the board sponsored legislation in 2013 to increase licensure requirements for sterile compounding pharmacies (SB 294, Chapter 565, Emmerson). The legislation expanded the definition of sterile compounding to include injectable medications, inhalation products and medication applied in the eyes. The law also eliminated accreditation by outside agencies as an alternative to licensure with annual board inspections, and the board began a massive upgrading of its sterile compounding regulations, a process that is nearing completion in late 2015.

The November 2013 enactment of the federal Drug Quality and Security Act (DQSA) responded to the 2012 compounding tragedy in a new way: this legislation created a new type of entity authorized to compound medications – the outsourcing facility. These generally large-scale production facilities are authorized to compound large quantities of medications for use by other entities, whereas a pharmacy generally compounds pursuant to a patient-specific prescription. Medications prepared by outsourcing facilities must be done under current good manufacturing practices (or cGMPs), which are more stringent than compounding requirements for sterile compounding pharmacies, since many patients in multiple locations can receive these medications that are not usually linked to patient-specific prescriptions.

Currently California is licensing as sterile compounding pharmacies federally licensed outsourcing facilities located within or shipping medication into California. This is increasingly losing its viability as a regulatory solution. First, it does not recognize the federal outsourcing requirements that permit large scale compounding. Second multiple states are moving to establish regulatory frameworks to license outsourcing facilities as separate entities, and some bar licensure of these facilities in their home states as sterile

compounding pharmacies. This is currently an issue in Mississippi, will and be an issue in July in New Jersey. Several other states have pending legislation in this area as well.

In 2015, the board sponsored legislation (SB 619, Morrell) to license outsourcing facilities as separate entities both within and outside California to ship into the state. This bill was held in suspense by the Senate Appropriations Committee. In 2016, the board seeks to resume pursuing regulation of outsourcing facilities as separate entities. The Senate Business and Professions Committee will evaluate outsourcing facilities as part of its evaluation of the impact of the DQSA during the board's sunset review. A legislative solution is likely to come as part of this review.

At the committee meeting

Ms. Herold explained that the sunset review committee staff indicated that establishing a licensing program for outsourcing facilities located within and outside California will be a sunset issue for the board to address. Ms. Herold foresees the board working with the committee staff to find a solution.

The committee heard public comment suggesting that any proposed legislation be specific when defining the provisions for a pharmacy and an outsourcing facility to do business at the same location.

Ms. Herold clarified that the board does not allow two licenses to share the same premises. Some rare exceptions include a 3PL and a wholesaler as well as a wholesaler and a veterinary retailer. Two different licensees need to have a hard wall between them, must have separate ingress and egress, and must maintain separate records.

2. Registration of Automated Delivery Devices in Use

Pharmacies are able to operate automated dispensing machines or devices in various settings away from the licensed pharmacy. This includes in:

- Skilled nursing homes and other health care facilities licensed under Health and Safety Code section 1250 (c), (d) or (k) (the devices are authorized under section 1261.6 of the Health and Safety Code, authority for pharmacies to do this in specific locations is specified in Business and Professions Code section 4119.1)
- Clinics licensed under section 4180 of the Business and Professions Code (the devices are authorized under section 4186) – these include licensed, nonprofit community or free clinics defined under Health and Safety Code 1204(a)(1), a clinic operated by a federally recognized Indian tribe or tribal organization referred to in Health and Safety Code section 1206(b), a clinic operated by a primary care community or free clinic operated on a separate premises from a licensed clinic and that is open no more than 20 hours per week as referred to in Health and Safety Code section 1206(h), a student

health center clinic operated by a public institution of higher education such as college health center as referred to in Health and Safety Code section 1206(j).

- Hospitals may use Pyxis or Pyxis-type machines throughout a hospital to store medication under application of provisions in Title 22 that allow drugs to be stored in nursing stations. The Pyxis and like devices are considered secured storage units for drugs.

The board has no idea how many of these machines are in use, where they are in use, or which pharmacy is responsible for any machine.

The demand for additional use of devices is growing. As scheduled earlier at this meeting, a pilot study is underway that if proven valuable, would allow patients to pick up medication from machines not specifically located in a pharmacy.

At the September 9, 2015, committee meeting, staff suggested that a simple registration be established for pharmacies that operate each of these machines that identifies their locations, as a beneficial step in board oversight and enforcement. The list could be updated as needed via form submission to the board by a pharmacy adding, moving or removing a machine. This registration could operate much like the off-site storage waivers for records waivers. Then at annual renewal of the pharmacy, the pharmacy would update or confirm the list of machines it operates and where each is located. Staff noted that a regulation or statutory amendment is likely needed to establish this requirement.

At the committee meeting

Dr. Gutierrez provided an overview of the background and Ms. Herold indicated that this proposal was one of the board's three recommendations in the sunset report.

There were no questions or comments.

e. Proposal for Routine Inspections of Pharmacies Every Four Years

The board's charge to regulate the pharmacy profession necessitates routine inspections of licensed facilities to confirm adherence to or identify failures in adherence to the requirements of pharmacy law. Failure to perform such inspections means that the board's enforcement program is reactive rather than proactive and relies solely on being advised of a potential violation of pharmacy law via a complaint or other information that would trigger an investigation.

For a number of years the board has wanted to inspect all facilities every three or four years. The board has been unable to complete these routine inspections of all facilities with any regularity, and in recent years has had to substantially reduce such inspections. While inspections are completed, inspections occur generally as part of the investigative process,

prior to issuance or renewal of a sterile compounding license or as part of probation monitoring.

All Inspections FY11-12 thru FY14-15 by Visit Type					
# of Inspections					
Inspection Type	FY11-12	FY12-13	FY13-14	FY14-15	Total
Routine	1730	1010	287	342	3369
Investigation	743	896	875	926	3440
Probation/PRP	258	228	139	227	852
Sterile Compounding	268	276	996	1067	2607
Other	34	39	32	26	131
Grand Total	3033	2449	2329	2588	10399

Mandatory inspections on a routine but random basis would enable the board to perform compliance inspections to educate licensees about pharmacy law as well as identify problems early to prevent more serious consumer issues from developing. Like all inspections, such inspections would be unannounced.

Compliance inspections provide an opportunity for board staff to answer questions about pharmacy law and to complete follow up inspections of facilities previously issued either citations or letters of admonishment to confirm compliance.

Mandatory inspections once every four years would be an alternative to our current practice of conducting inspections principally to investigate problems (or inspect sterile compounders).

The board currently has 6,572 community pharmacies licensed in California. Some of these pharmacies have never been inspected by the board. The creation of a statutory mandate directing the board to perform inspections of all pharmacies every four years would require approximately 1,650 routine inspections annually. Over the last two years, the board completed an average of 1,215 inspections annually (routine plus investigation inspections).

At the committee meeting

Dr. Gutierrez provided an overview of the proposal. Ms. Herold advised that the board needs to commit to performing the proposed inspections. The inspections would allow the board inspectors to work proactively as a resource for pharmacies instead of initiating inspections reactively based on complaints.

A motion was made to create a statutory mandate to complete random, unannounced routine inspections of pharmacies once every four years.

The committee heard public comment about whether the motion was intended to include all facilities the board licenses or just pharmacies and whether the motion was intended to include nonresident pharmacies.

Ms. Herold clarified that the motion was intended to include resident pharmacies and non-resident sterile facilities only. Ms. Herold stated that the National Association of Boards of Pharmacy is conducting inspections on nonresident pharmacies and that the board has staff in place to review the reports if the pharmacy is licensed in California. The board wants to complete the inspections without increasing the inspector staff or raising fees.

Committee Recommendation:

Create a statutory mandate to complete random, unannounced routine inspections of resident pharmacies once every four years.

f. Discussion on Items in the News:

1. “Preventing Diversion in the ED” from www.pppmag.com, November 2015

The article in **Attachment 4** was added to the agenda by Board President and Committee Chair Gutierrez. In the article, the author asserts that drug diversion by health care workers is quite common. The article reviews the techniques health care workers use to divert drugs and suggests multifaceted approaches for preventing and identifying diversion.

This item was informational only. There were no questions or comments.

2. Settlement Agreement between the Drug Enforcement Administration and Massachusetts General Hospital for Drug Diversion

Earlier this fall, the U.S. Drug Enforcement Administration alleged that Massachusetts General Hospital failed to make and keep records required by the Controlled Substances Act, and failed to provide effective controls and procedures to guard against theft and loss of controlled substances from October 4, 2011 through April 1, 2015. On September 28, 2015, Massachusetts General Hospital agreed to pay a settlement amount of \$2,300,000.

A copy of the settlement is provided in **Attachment 5**.

This item was informational only. There were no questions or comments.

g. Review of Controlled Substances Losses Reported to the Board

Board discussions in recent meetings have included drug thefts from automated drug dispensing machines. Board staff was recently asked to tabulate how many controlled substances losses have been reported to the board from automated dispensing machines.

While there is no category listed on the DEA 106 report to capture this specific type of data, board staff reviewed all loss reports since January 1, 2015 and identified the following losses that had been identified in automated dispensing machines. When reviewing the data keep in mind that:

1. The amount of controlled substances reported lost is usually lower than the actual amount of loss determined at the end of an investigation, and
2. Without a reporting category for this type of loss, some losses from automated dispensing machines could be reported under other categories.

Reports of Losses Related to Automatic Dispensing Machines (ADMs: Pyxis, Omnicell, Acudose, etc.) January 1, 2015 - November 30, 2015	Total # Reports	ADM Losses - Percent of Total Reports	Total Dosage Units Lost
180	2,267	8%	6,714

*total dosages (mLs converted into 5mL dosage units and added to solids)

Board of Pharmacy License Type for ADM Losses	# of Reports
Hospitals	177
Pharmacies	3
Total	180

Type of loss	# of Reports
Pilferage/Possible Pilferage or Not following proper procedures by nurse(s)	97
Unknown cause	78
Lost in transit to/from Automatic Dispensing Machine	2
Automatic Dispensing Machine error	1
Possible Pilferage by Pharmacy Technician	1
Possible Theft by patient	1
Total	180

The board will begin reporting all controlled substances losses reported to the board at each committee meeting.

At the committee meeting

Dr. Gutierrez provided an overview and asked Ms. Sodergren to provide an analysis of the data. Ms. Sodergren explained that the Total Dosage Units Lost data was skewed by one large loss of over 4,600 units. If the one large loss is removed, the average loss is actually about 11 dosage units.

Regarding types of loss, Ms. Sodergren clarified that losses where the type of loss was unknown were very small. The highest loss was 25 dosage units, but the majority of losses were 5 dosage units or fewer. It doesn't appear that there are significant losses where pharmacies are unable to identify the cause.

The committee heard public comment regarding the creation of a so-called "safe harbor" wherein a PIC would not be disciplined if they could prove they followed established guidelines/best practices for detecting drug diversion.

Dr. Gutierrez asked why vendors do not do a better job of educating their customers about the systems and best practices. A member of the public commented that some vendors provide education, but some customers might become overwhelmed. He indicated that canned reports are available, but staff has to review them and decide which best fit their needs.

Committee Recommendation:

Invite Vendors to come to the next enforcement and compounding committee meeting to discuss reports/best practices for diversion detection.

h. Enforcement Options for Patient Consultation Violations

Nearly 25 years ago, the Board of Pharmacy promulgated regulations to require pharmacists to consult with patients every time they receive a medication for the first time. The board included in the regulation additional occasions where a pharmacist must consult a patient – where the patient has questions or the pharmacist believes a medication warrants consultation. A copy of the requirement is provided in **Attachment 6**.

Sometimes California's requirements are confused with national requirements enacted about the same time by CMS for Medicare patients in what was known as "OBRA 90." However, California's requirements were actually adopted before OBRA 90's requirements. The OBRA 90 requirements provided that Medicare patients be offered consultation when they receive

medication for the first time. So California's requirements, requiring the pharmacist to initiate consultation, were stronger and broader than the OBRA 90 requirements in that they pertained to all patients, not just those whose medications were paid for by Medicare, establishing one standard of care for all patients in California.

After approval of California's patient consultation requirements, the board also delayed implementation of patient consultation at the request of the profession because pharmacists stated they could not provide consultation without the aid of pharmacy technicians. So the approved patient-consultation regulation was delayed so that the board could secure statutory authority and then promulgate regulations to establish the licensure of pharmacy technicians to "free" the pharmacist to provide consultation.

California's requirement is for the pharmacist to consult the patient – not to offer to consult. When doing the consultation rulemaking, the board emphasized that consultation was to be initiated by the pharmacist, and that any denial of the consultation must be made directly to the pharmacist, other staff (e.g., pharmacy technicians or ancillary staff) were not to screen for consultation by asking if the patient wanted to speak to the pharmacist or had questions about the medication. Consultation was required whenever the patient or the patient's agent was present in the pharmacy to receive the consultation.

Over the years, the board has added other enhancements to help ensure patients receive meaningful consultation, including a "Notice to Consumers" poster that must be posted in a pharmacy that specifically states the pharmacist must consult with each patient about his or her new medication, and lists the 5 questions a patient should understand before taking a prescription medication.

More recently in promulgating the requirements for patient-centered labels, the board required that oral consultation services be available in 12 languages to aid limited-English speaking patients in better understanding how to take their prescription medication.

Over the years, the board has enforced its patient consultation requirements in various ways. Initially it was one of the first violations for which the board used its citation and fine authority. In recent years, the board has typically assessed fines of approximately \$1,000 when it observes failure to consult during an inspection. Where a medication error has occurred and consultation was not provided, the board generally issues a higher fine.

In 2011, board staff began working on a project with three California district attorneys' offices to aid in the board's enforcement of patient consultation. Using the state's unfair business practices statute in Business and Professions Code section 17200, the DAs' offices were able to assess higher fines for failure to consult. Additionally, the DAs' offices used undercover investigators to pass prescriptions, an action the board has not done.

The DAs' investigations have resulted in more substantial fines to three pharmacy chains where investigations have been completed – CVS (2013, \$658,500), Rite Aid (2014, \$498,250) and recently Walgreens (2015, \$502,000).

At the September 9, 2015, committee meeting, the committee heard questions and comments from the public regarding whether the board can prohibit the use of a system that requires a patient to accept or decline patient consultation in advance of payment. The committee requested that the Communication and Public Education committee focus on consumer education and why patient consultation is important.

At the committee meeting

This item was added to the agenda in the event the committee wished to discuss sanctions for failure to consult, or to wait for the Communication and Public Education Committee to complete its work on reviewing consultation matters before discussing sanctions.

Dr. Gutierrez indicated that it was her understanding that this item would be deferred to the Communication and Public Education Committee for follow up.

Ms. Herold verified that the Communication and Public Education Committee was given general responsibility for uncovering the reasons why consultations aren't being performed. She believed it was appropriate to wait until the Communication and Public Education Committee finishes its work before the Enforcement and Compounding Committee proceeds any further.

i. Discussion and Update to the Board's Emergency Response Policy

On September 15, 2015, the board held an Emergency Board Meeting in response to the wildfires in Lake and Napa counties. In light of the recent use of the policy it was brought to the board for evaluation and assessment to determine if changes to the policy are necessary.

At the October 28-29, 2015 board meeting, this item was referred to the enforcement committee for discussion.

Attachment 7 contains the board's current emergency response policy, an excerpt of the board meeting minutes where the policy was adopted and a copy of Business and Professions Code section 4062.

At the committee meeting

Staff Counsel, Laura Freedman, provided some background and discussed some of the challenges of the current policy. The current policy suggests that a meeting wouldn't need to be held pursuant to the open meeting act. She advised amending the opening statement

to specify that if the board is not able to establish a quorum, three members would be able to exercise the board’s authority pursuant to Business and Professions Code section 4062.

Ms. Freedman also stated that the board has other options including delegating the authority to a specific board member, perhaps the board president. She recommended that if the board chose that option, that it limit the authority to 14-30 days.

Committee Recommendation:

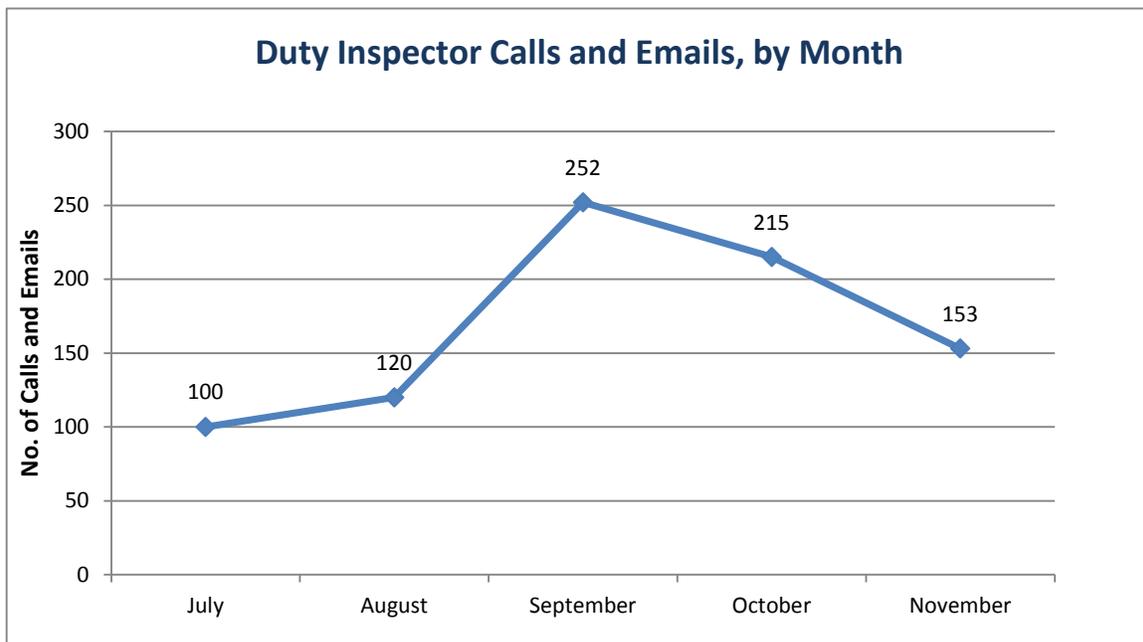
Modify board policy to delegate its authority pursuant to Business and Professions Code section 4062 to the board president for a period of 30 days.

j. Review of Duty Inspector Activities

Attachment 8 shows the number of pharmacy inspector calls handled by the board’s Complaint Unit during the first half of the 2015-2016 fiscal year.

Between July 1, 2015 and November 2015, board inspectors responded to 840 calls, an average of 168 calls each month. The highest month was September, with 252 calls. July was the lowest month, with 100 calls.

Chart: All Inspector Calls, Trends by Month



In September, the board expanded its inspector answer program in two ways. First, the board tripled the hours inspectors take phone calls from six hours each week to 16 hours. Second, the board added the "Ask.Inspector" email box. Board inspectors respond to emails five days a week. Additionally, in September, licensees were sent a Subscriber Alert to let them know of the expanded inspector hours.

The addition of the added call hours and the email box resulted in a significant increase in activity. In September, inspector requests more than doubled from August. There were 120 calls in August and 252 in September, an increase of 115 percent. In September and October, inspectors handled more than 200 calls each month. In October and November, the number of calls declined although not back to the August levels.

The board's public information officer began work to establish an online resource directory of frequently asked questions (FAQ). The goal is to put many questions and answers online so individuals can find their own answers.

More data is provided in **Attachment 8**.

At the committee meeting

Dr. Gutierrez reviewed duty inspector activity statistics.

Ms. Herold indicated that the new Public Information Officer was working on an online FAQ directory. She estimated the FAQ's would be available in 30-90 days.

There were no questions or comments.

k. Enforcement Statistics

Attachment 9 includes the second quarter report of the Enforcement Statistics and SB 1441 Program Statistics.

l. Future Committee Meeting Dates

The committee has established the following enforcement committee meeting dates:

March 2, 2016
June 1, 2016
August 31, 2016

III.COMPOUNDING MATTERS

a. 2015 FDA Intergovernmental Meeting on Drug Compounding and Drug Supply Chain Security Held in November 2015

On November 16 and 17, the Food and Drug Administration (FDA) convened the 2015 Intergovernmental Working Meeting on Drug Compounding and Supply Chain Security. This meeting had representatives from about 45 states and was intended to exchange information with states as the 2013 Drug Quality Security Act is being implemented.

Executive Officer Herold and a deputy director from the California Department of Public Health were California's attendees.

The purpose of the meeting was to update states on emerging FDA policy regarding sterile compounding, outsourcing facilities and supply chain security requirements (the latter are the provisions that preempted California's e-pedigree requirements).

Most of the meeting focused on compounding/outsourcing requirements, with the last quarter of the meeting focusing on the licensing requirements for wholesalers and third-party logistics providers. Ms. Herold provided presentations during both segments.

Attachment 10 contains information on two presentations provided during the two-day meeting. Below is an overview of the agenda:

1. Compounding Regulatory Policy Update
2. Draft Standard Memorandum of Understanding between FDA and the States
3. Information Sharing and Disclosures (between state agencies and FDA)
4. A Comparison of US Pharmacopeial Convention General Chapter 797 to the Current Good Manufacturing Practice Regulations Enforced by DEA
5. Inspections of Sterile compounding Facilities and Enforcement
6. State Handling of Outsourcing Facilities
7. Overview of DSCSA Implementation
8. Wholesaler Distributor and 3PL Provider Licensing
9. FDA and State Collaboration

At the committee meeting

Ms. Herold discussed and highlighted information from the FDA meeting. Specifically, Ms. Herold indicated that the FDA was inspecting pharmacies and notifying the state boards of pharmacy when follow-up was needed. Additionally, Ms. Herold stated that some states were inspecting outsourcing facilities using USP 797 (including California) although the FDA was regulating outsourcing facilities using Current Good Manufacturing Practices (CGMPs). The board has a bill that will become a sunset issue regarding the future regulation of outsourcing facilities.

Ms. Herold noted that many states were attempting to catch up to the new federal requirements and many didn't have requirements to fingerprint their applicants. This highlights this disparity in regulation and oversight when shipping across state lines.

Dr. Gutierrez asked for clarification on USP 797. Ms. Herold stated that 797 is a guideline that the FDA allows to be enforceable. Years ago, the board asked if the state could require 797 by itself, but the board's attorneys determined that the germane parts of 797 would have to be placed into law. The board is almost finished adding those germane parts of 797 to state law.

There were no public comments.

b. Development of a Waiver Process from Building Standards Requirements Contained in Proposed Title 16 California Code of Regulations Sections 1751 et seq.

During the October 2015 board meeting, the board discussed and took action on proposed changes to compounding requirements. As part of this discussion, the board discussed the need to establish a waiver requirement for some of the structural requirements. Suggested components to facilitate such a process were included in the most recent modifications to the proposed regulation (where the comment period ended December 5). As proposed in the regulation (as subdivision 1735.6(f) and in 1751.4(l)), the waiver request shall:

1. be made in writing
2. identify the provision(s) requiring physical construction, alteration, or improvement
3. contain a timeline for any such change

Consistent with the proposed language which was noticed for comment, board staff has worked on development of a specific format upon adoption of the language by the board. Board review of the last proposed modifications to the compounding regulation will be scheduled for this board meeting.

This item was informational only. There were no questions or comments.

c. Review of "USP <800>: Key Considerations and Changes for Health Systems," Hospital Pharmacy 2015; 501(1):941-949

On March 28, 2014, the United States Pharmacopeia and the National Formulary (USP-NF) published USP General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings, as open for public comment in the USP Pharmacopeial Forum (PF) 40(3). USP <800> serves as a new standard to guide the handling of hazardous drugs in order to protect patients, health care personnel, and the environment. USP <800> describes hazardous drug handling related to the receipt, storage, compounding, dispensing, and administration and disposal of both

sterile and nonsterile products and preparations. According to this review, “Although complying with USP <800> may seem to be a daunting task, it can be manageable if approached in a systematic organized way. “

The paper in **Attachment 11** explores some of the more important aspects of the regulations in USP <800>.

The final version of the chapter was published on Feb 1, 2016 and USP states it will become enforceable on July 1, 2018.

This item was informational only. There were no questions or comments.

The full minutes of the December 14, 2015 Enforcement and Compounding Committee meeting, are provided in **Attachment 12**.

Attachment A

CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016

Prepared by:

Deborah Dowell, MD from the Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC
Tamara M. Haegerich, PhD from the Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC
Roger Chou, MD from Oregon Health and Science University

Summary

This guideline provides recommendations for primary care providers who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses 1) when to initiate or continue opioids for chronic pain; 2) opioid selection, dosage, duration, follow-up, and discontinuation; and 3) assessing risk and addressing harms of opioid use. CDC developed the guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, and recommendations are made on the basis of a systematic review of the scientific evidence while considering benefits and harms, values and preferences, and resource allocation. CDC consulted with experts knowledgeable in the areas of opioid prescribing, addiction, substance use disorder treatment, and pain management to interpret the evidence and inform the recommendations and provided opportunities for stakeholder review, constituent engagement, and peer review. It is important that patients receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options. This guideline is intended to improve communication between providers and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including abuse, dependence, overdose, and death.

Introduction

Background

Opioids are commonly prescribed for pain. An estimated 20% of patients presenting to physician offices with noncancer pain symptoms or pain-related diagnoses (including acute and chronic pain) receive an opioid prescription (1). In 2012, health care providers wrote 259 million prescriptions for opioid pain medication, enough for every adult in the United States to have a bottle of pills (2). Opioid prescriptions per capita increased 7.3% from 2007 to 2012, with opioid prescribing rates increasing more for family practice, general practice, and internal medicine compared with other specialties (3). Rates of opioid prescribing vary greatly across states in ways that cannot be explained by the underlying health status of the population, highlighting the lack of consensus among providers on how to use opioid pain medication (2).

Prevention, assessment, and treatment of chronic pain are challenges for health providers and systems. Pain might go unrecognized, and patients can be at risk for inadequate pain treatment, particularly racial and ethnic minorities, women, the elderly, persons with cognitive impairment, and those with cancer and at the end of life. (4). Patients should receive appropriate pain treatment based on a careful consideration of the benefits and risks of treatment options. Chronic pain has been variably defined but is considered within this guideline as pain that typically lasts >3 months or past the time of normal tissue healing (5). Chronic pain can be the result of an underlying medical disease or condition, injury, medical treatment, inflammation, or an unknown cause (4). Estimates of the prevalence of chronic pain vary, but it is clear that the number of persons experiencing chronic pain in the United States is substantial. The 1999–2002 National Health and Nutrition Examination Survey estimated a prevalence of current widespread or localized pain lasting at least 3 months of 14.6% (6). The overall prevalence of common, predominantly musculoskeletal pain conditions that can be chronic (e.g., arthritis, rheumatism, chronic back or neck problems, and frequent severe headaches) was estimated at 43% among adults in the United States (7) based on a survey conducted during 2001–2003. Most recently, analysis of data from the 2012 National

Health Interview Study revealed an estimated prevalence of daily pain of 11.2% (8). It is hard to estimate the number of persons who could potentially benefit from opioid pain medication long term. Although evidence supports short-term efficacy of opioids for reducing pain and improving function in noncancer nociceptive and neuropathic pain in trials lasting <16 weeks (9), few studies to assess the long-term benefits of opioids for chronic pain (pain lasting >3 months) with outcomes examined at least 1 year later have been conducted (10). On the basis of data available from health systems, researchers estimate that 9.6 to 11.5 million adults, or approximately 3%–4% of the adult U.S. population, were prescribed long-term opioid therapy in 2005 (11).

Opioid pain medication use presents serious risks, including opioid use disorder (opioid abuse or dependence, sometimes referred to as addiction) and overdose. Since 1999, more than 140,000 persons have died from overdose related to opioid pain medication in the United States (12). In the past decade, while the death rate for the top leading causes of death such as heart disease and cancer has decreased substantially, the death rate associated with opioid pain medication has increased substantially (13). More than 16,000 deaths occurred in 2013, four times the number of overdose deaths related to these drugs in 1999 (12). Sales of opioid pain medication have increased in parallel with opioid-related overdose deaths (14). The Drug Abuse Warning Network estimated that >420,000 emergency department visits were related to the misuse or abuse of narcotic pain relievers in 2011, the most recent year for which data are available (15). While clinical criteria have varied over time, opioid use disorder is a problematic pattern of opioid use leading to clinically significant impairment or distress. This disorder is manifested by specific criteria such as unsuccessful efforts to cut down or control use and use resulting in social problems and a failure to fulfill major role obligations at work, school, or home (16). In 2013, an estimated 1.9 million persons abused or were dependent on prescription opioid pain medication (based on DSM-IV criteria) (17). Having a history of a prescription for an opioid pain medication increases the risk for overdose and opioid use disorder (18–20), highlighting the value of guidance on safer prescribing practices for providers.

This guideline provides recommendations for the prescribing of opioid pain medication by primary care providers for chronic pain (i.e., pain conditions that typically last longer than 3 months or past the time of normal tissue healing) in outpatient settings outside of active cancer treatment, palliative care, and end-of-life care. Although the guideline does not focus broadly on pain management, appropriate use of long-term opioid therapy must be considered within the context of all pain management strategies (including nonopioid pain medications and nonpharmacologic treatments). Recommendations are based on a systematic review of the best available evidence, along with consultation from an expert panel. The guideline is intended to ensure that providers and patients consider safer and more effective treatment, improve patient outcomes such as pain and function, and reduce the number of persons who develop opioid use disorder, overdose, or experience other adverse events related to these drugs. The guideline offers recommendations rather than prescriptive standards; providers should consider the circumstances and unique needs of each patient.

Rationale

Primary care providers report concern about opioid pain medication misuse, find managing patients with chronic pain stressful, express concern about patient addiction, and report insufficient training in prescribing opioids (21). Across specialties, physicians believe that opioid pain medication can be effective in controlling pain but agree that physical dependence, tolerance, and addiction are common consequences of prolonged use; nevertheless, long-term opioid therapy often is overprescribed for patients with chronic noncancer pain (22). These attitudes and beliefs, combined with increasing trends in opioid use disorder and opioid-related overdose, underscore the need for better provider guidance on opioid prescribing. Clinical practice guidelines focused on prescribing can improve provider knowledge, change prescribing practices (23), and ultimately benefit patient health.

Professional organizations, states, and federal agencies have developed guidelines on opioid prescribing (e.g., the American Pain Society/American Academy of Pain Medicine, 2009; the Washington Agency Medical Directors Group, 2015; and the U.S. Department of Veterans Affairs/Department of Defense, 2010) (24–26). Existing guidelines share some common elements, including dosing thresholds, cautious titration, and risk mitigation strategies such as using risk assessment tools, treatment agreements, and urine drug testing. However, there is considerable variability in the specific recommendations (e.g., range of dosing thresholds of 90 morphine milligram equivalents (MME)/day to 200 MME/day), audience (e.g., primary care providers versus specialists), use of evidence (e.g., systematic review versus expert opinion), and rigor of methods for addressing conflict of interest (27). Most guidelines, especially those that are not based on evidence from scientific studies published in 2010 or later, also do not reflect the most recent scientific evidence about risks related to opioid dosage.

This CDC guideline offers clarity on recommendations based on the most recent scientific evidence, informed by expert opinion, with stakeholder and constituent input considered. Scientific research has identified high-risk prescribing practices that have contributed to the overdose epidemic (e.g., high-dose prescribing, overlapping opioid and benzodiazepine prescriptions, and extended-release/long-acting [ER/LA] opioids for acute pain) (20,28,29). Using guidelines to address problematic prescribing has the potential to optimize care and improve patient safety based on evidence-based practice (23), as well as reverse the cycle of opioid pain medication abuse that contributes to the overdose epidemic.

Scope and Audience

This guideline is intended for primary care providers (e.g., family physicians and internists) who are treating patients with chronic pain (i.e., pain lasting >3 months or past the time of normal tissue healing) in outpatient settings. Prescriptions by primary care providers account for nearly half of all dispensed opioid prescriptions, and the growth in prescribing rates among these providers has been above average (3). Although the transition from use of opioid therapy for acute pain to chronic pain is hard to predict and identify, the guideline is intended to inform providers who are considering prescribing opioid pain medication for painful conditions that can or have become chronic.

This guideline is intended to apply to patients aged ≥ 18 years with chronic pain outside of palliative and end-of-life care. For this guideline, palliative care is defined in a manner consistent with that of the Institute of Medicine as care that provides relief from pain and other symptoms, supports quality of life, and is focused on patients with serious advanced illness. *Palliative care* can begin early in the course of treatment for any serious illness that requires excellent management of pain or other distressing symptoms (30). End-of-life care is defined as care for persons with a terminal illness or at high risk for dying in the near future in hospice care, hospitals, long-term care settings, or at home. Patients within the scope of this guideline include cancer survivors with chronic pain who have completed cancer treatment, are in clinical remission, and are under cancer surveillance only. The guideline is not intended to apply to patients in treatment for active cancer. The guideline is not intended for patients undergoing active cancer treatment, palliative care, or end-of-life care because of the unique therapeutic goals, ethical considerations, opportunities for medical supervision, and balance of risks and benefits with opioid therapy in such care. The recommendations address the use of opioid pain medication in certain special populations (e.g., older adults and pregnant women) and in populations with conditions posing special risks (e.g., a history of substance use disorder).

The recommendations are not intended to provide guidance on use of opioids as part of medication-assisted treatment for opioid use disorder. Some of the recommendations might be relevant for acute care settings or other specialists, such as emergency physicians or dentists, but use in these settings or by other specialists is not the focus of this guideline. Readers are referred to other sources for prescribing recommendations within acute care settings and in dental practice, such as the American College of Emergency Physicians' guideline for prescribing of opioids in the emergency department (31); the American Society of Anesthesiologists' guideline for acute pain management in the perioperative setting

(32); the Washington Agency Medical Directors' Group Interagency Guideline on Prescribing Opioids for Pain, Part II: Prescribing Opioids in the Acute and Subacute Phase (26); and the Pennsylvania Guidelines on the Use of Opioids in Dental Practice (33). In addition, given the challenges of managing the painful complications of sickle cell disease, readers are referred to the NIH National Heart, Lung, and Blood Institute's Evidence Based Management of Sickle Cell Disease Expert Panel Report for management of sickle cell disease (34).

Guideline Development Methods

Guideline Development Using the Grading of Recommendations Assessment, Development, and Evaluation Method

CDC developed this guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (<http://www.gradeworkinggroup.org/>). This method specifies the systematic review of scientific evidence and offers a transparent approach to grading quality of evidence and strength of recommendations. The method has been adopted and translated by the CDC Advisory Committee for Immunization Practices (ACIP) (35). CDC has applied the ACIP translation of the GRADE framework in this guideline. Within the ACIP GRADE framework, the body of evidence is categorized in a hierarchy. This hierarchy reflects degree of confidence in the effect of a clinical action on health outcomes. The categories include type 1 evidence (randomized controlled trials or overwhelming evidence from observational studies), type 2 evidence (randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies), type 3 evidence (observational studies or randomized controlled trials with notable limitations), and type 4 evidence (clinical experience and observations, observational studies with important limitations, or randomized controlled trials with several major limitations). Type of evidence is categorized by study design as well as limitations in study design or implementation, imprecision of estimates, variability in findings, indirectness of evidence, publication bias, the magnitude of treatment effects, dose-response gradient, and a constellation of plausible biases that could change observations of effects. Type 1 evidence indicates that one can be very confident that the true effect lies close to that of the estimate of the effect; type 2 evidence means that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; type 3 evidence means that confidence in the effect estimate is limited and the true effect might be substantially different from the estimate of the effect; and type 4 evidence indicates that one has very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of the effect (35,36). When no studies are present, evidence is considered to be insufficient. The ACIP GRADE framework constructs recommendations in two categories, Category A and Category B. Four major factors determine the category of the recommendation: the quality of evidence, the balance between desirable and undesirable effects, values and preferences, and resource allocation (cost). Category A recommendations apply to all persons in a specified group and indicate that most patients should receive the recommended course of action. Category B recommendations indicate that there should be individual decision making; different choices will be appropriate for different patients, so providers must help patients arrive at a decision consistent with patient values and preferences, and specific clinical situations (35). According to the GRADE methodology, a particular quality of evidence does not necessarily imply a particular strength of recommendation (36–38). Category A recommendations can be made based on type 3 or type 4 evidence when the advantages of a clinical action greatly outweigh the disadvantages based on a consideration of benefits and harms, values and preferences, and costs. Category B recommendations are made when the advantages and disadvantages of a clinical action are more balanced. GRADE methodology is discussed extensively elsewhere (35,37,39).

A previously published systematic review sponsored by the Agency for Healthcare Research and Quality (AHRQ) on the effectiveness and risks of long-term opioid treatment of chronic pain (10,40)

initially served to directly inform the recommendation statements. This systematic clinical evidence review addressed the effectiveness of long-term opioid therapy for outcomes related to pain, function, and quality of life; the comparative effectiveness of different methods for initiating and titrating opioids; the harms and adverse events associated with opioids; and the accuracy of risk-prediction instruments and effectiveness of risk mitigation strategies on outcomes related to overdose, addiction, abuse, or misuse. For the current guideline development, CDC conducted additional literature searches to update the evidence review to include more recently available publications and to answer an additional clinical question about the effect of opioid therapy for acute pain on long-term use (See Online Appendix 1: Clinical Evidence Review, available in the “Supporting Documents” section of the docket). CDC developed GRADE evidence tables to illustrate the quality of the evidence for each clinical question.

As identified in the AHRQ-sponsored clinical evidence review, the overall evidence base for the effectiveness and risks of long-term opioid therapy is low in quality per the GRADE criteria. Thus, contextual evidence that provides information about alternatives to long-term opioid therapy and the epidemiology of opioid pain medication overdose is critical for informing the recommendations. Further, as elucidated by the GRADE Working Group, supplemental information on provider and patient values and preferences and resource allocation can inform judgments of benefits and harms and be helpful for translating the evidence into recommendations. CDC conducted a contextual evidence review to supplement the clinical evidence review based on systematic searches of the literature. The review focused on the following four areas: effectiveness of alternative treatments (i.e., nonpharmacologic and nonopioid pharmacologic treatments); benefits and harms related to opioid therapy (found in epidemiology rather than the clinical randomized trial literature related to specific opioid pain medications, high-dose opioid therapy, co-prescription of opioids with other controlled substances, duration of opioid use, special populations, risk stratification/mitigation approaches, and effectiveness of treatments for addressing potential harms of opioid therapy); provider and patient values and preferences; and resource allocation. CDC constructed narrative summaries of this contextual evidence and used the information to support the clinical recommendations (See Contextual Evidence Review, available in the “Supporting Documents” section of the docket).

On the basis of a review of the clinical and contextual evidence (review methods described in more detail in subsequent sections), CDC drafted recommendation statements focused on determining when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. CDC then solicited expert opinion in the form of individual ratings, discussions, and written comment to help refine the recommendations.

Solicitation of Expert Opinion

CDC invited a core group of experts (the Core Expert Group [CEG]) to assist in reviewing the evidence and providing perspective on how CDC translated the evidence into draft recommendations. Experts provided individual consultation. The group was composed of subject matter experts, representatives of primary care professional societies and state agencies, and an expert in guideline development methodology.* CDC identified subject matter experts with high scientific standing; appropriate academic and clinical training and relevant clinical experience; and proven scientific excellence in opioid prescribing, addiction, substance use disorder treatment, and pain management. CDC identified representatives from leading primary care professional organizations to represent the audience for this guideline. Finally, CDC identified state agency officials and representatives based on their experience with state guidelines for opioid prescribing that were developed with multiple agency stakeholders and informed by scientific literature and existing evidence-based guidelines.

Prior to their participation, CDC asked potential experts to reveal possible conflicts of interest such as financial relationships with industry, intellectual preconceptions, or previously stated public positions. Experts could not serve if they held conflicts that could be anticipated to have a direct and predictable effect on the recommendations. CDC excluded experts if there was a financial or promotional relationship with a company that makes a product that might be affected by the guideline. CDC reviewed potential nonfinancial conflicts carefully (e.g., intellectual property, travel, public statements or positions such as congressional testimony) to determine if the activities would have a direct and predictable effect on the recommendations. CDC determined the risk of these types of activities to be minimal for the identified experts. All experts completed a statement certifying that there was no potential or actual conflict of interest. Activities that did not pose a conflict (e.g., participation in Food and Drug Administration [FDA] activities or other guideline efforts) are disclosed.

The experts reviewed written summaries of the scientific evidence (both the clinical and contextual evidence reviews conducted for this guideline) and CDC's draft recommendation statements. Experts provided individual ratings for each draft recommendation statement based on the balance of benefits and harms, evidence strength, certainty of values and preferences, cost, recommendation strength, rationale, importance, clarity, and ease of implementation. CDC convened experts at an in-person meeting June 23–24, 2015, in Atlanta, Georgia, to seek the individual views of the experts on the evidence and draft recommendations. The experts provided their individual opinions at the meeting. Experts did not vote on the recommendations or seek to come to a consensus on the recommendations to be included in the guideline; decisions about recommendations to be included in the guideline were made by CDC. At the meeting, CDC noted experts' comments and any dissenting opinions on the recommendations. After revising the guideline, CDC sent it to the experts for review and asked for individual written comments; CDC reviewed these written comments and considered them when making further revisions to the guideline. Experts did not review the latest version of the guideline, or provide approval for the recommendations provided within.

Federal Partner Engagement

Given the scope of this guideline and the interest of agencies across the federal government in appropriate pain management, opioid prescribing, and related outcomes, CDC invited its National Institute of Occupational Safety and Health and CDC's federal partners to observe the expert meeting and provide written comments on the full guideline after the meeting; CDC reviewed comments and incorporated suggestions. Interagency collaboration will be critical for translating these recommendations into clinical practice. Federal partners included representatives from the Substance Abuse and Mental Health Services Administration, the National Institute on Drug Abuse, FDA, the U.S. Department of Veterans Affairs, the U.S. Department of Defense, the Office of the National Coordinator for Health Information Technology, the Centers for Medicare and Medicaid Services, the Health Resources and Services Administration, AHRQ, and the Office of National Drug Control Policy.

Stakeholder Comment

Given the importance of the guideline for a wide variety of stakeholders, CDC designated a Stakeholder Review Group (SRG) to provide comment so that CDC could consider modifications that would improve the recommendations' specificity, applicability, and ease of implementation. The SRG included representatives from professional organizations that represent specialties that commonly prescribe opioids (e.g., pain medicine, physical medicine and rehabilitation), delivery systems within which opioid prescribing occurs (e.g., hospitals), and representation from community organizations with interests in pain management and opioid prescribing.* CDC identified representatives from each of the SRG organizations and provided a copy of the guideline for comment. Once input was received from the full SRG, CDC reviewed all comments individually and carefully considered them when revising the guideline.

Peer Review

Peer review requirements applied to this guideline because it provides influential scientific information that could have a clear and substantial impact on public- and private-sector decisions. Three experts independently reviewed the guideline to determine the reasonableness of recommendations and ensure that scientific uncertainties were clearly identified.* CDC selected peer reviewers based on expertise, diversity of scientific viewpoints, and independence from the guideline development process. CDC assessed and managed potential conflicts of interest using a similar process to that used with the CEG members. No financial interests were identified in the disclosure and review process, and nonfinancial activities were determined to be of minimal risk; thus, no significant conflict of interest concerns were identified. CDC placed the names of peer reviewers on the CDC and the National Center for Injury Prevention and Control Peer Review Agenda websites that are used to provide information about the peer review of influential documents. CDC reviewed peer review comments and revised the guideline.

Constituent Engagement

To obtain perspectives from constituents, including providers and prospective patients, CDC convened a constituent engagement webinar and circulated information about the webinar in advance through announcements to partners. CDC hosted the webinar on September 16 and 17, 2015, provided information about the methodology for developing the guideline, and presented the key recommendations. A fact sheet was posted on the CDC Injury Center website summarizing the guideline development process and clinical practice areas addressed in the guideline; instructions were included on how to submit comments via email. CDC received comments during and for 2 days following the webinar. Comments were reviewed individually and carefully considered when revising the guideline.

Clinical Evidence Review

Primary Clinical Questions

For this guideline, CDC addressed five primary clinical questions regarding the effectiveness, benefits, and harms of long-term opioid therapy for chronic pain through systematic reviews of the scientific evidence. Long-term opioid therapy is defined as use of opioids on most days for >3 months. A previously published AHRQ-funded systematic review on the effectiveness and risks of long-term opioid therapy for chronic pain comprehensively addressed four clinical questions (10,40). CDC, with the assistance of a methodology expert, searched the literature to identify newly published studies on these four original questions. CDC subsequently developed a fifth clinical question (last in the series below), and in collaboration with a methodologist conducted a systematic review of the scientific evidence to address it. In brief, five clinical questions were addressed:

- The effectiveness of long-term opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for long term (>1 year) outcomes related to pain, function, and quality of life, and how effectiveness varies according to the type/cause of pain, patient demographics, and patient comorbidities (Key Question 1; KQ1).
- The risks of opioids versus placebo or no opioids on abuse, addiction, overdose, and other harms, and how harms vary according to the type/cause of pain, patient demographics, patient comorbidities, and dose (KQ2).
- The comparative effectiveness of opioid dosing strategies (different methods for initiating and titrating opioids; immediate-release versus ER/LA opioids; different ER/LA opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled, continuous versus as-needed dosing; dose escalation versus dose maintenance; opioid rotation versus maintenance; different strategies for treating acute exacerbations of chronic pain; decreasing opioid doses or tapering off versus continuation; and different tapering protocols and strategies) (KQ3).

- The accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse; the effectiveness of risk mitigation strategies (use of risk prediction instruments); effectiveness of risk mitigation strategies including opioid management plans, patient education, urine drug testing, prescription drug monitoring program (PDMP) data, monitoring instruments, monitoring intervals, pill counts, and abuse-deterrent formulations for reducing risk for opioid overdose, addiction, abuse, or misuse; and the comparative effectiveness of treatment strategies for managing patients with addiction (KQ4).
- The effects of prescribing opioid therapy versus not prescribing opioid therapy for acute pain on long-term use (KQ5).

The review was focused on the effectiveness of long-term opioid therapy on long-term (>1 year) outcomes related to pain, function, and quality of life to ensure that findings are relevant to patients with chronic pain and long-term opioid prescribing. For opioid-related harms (overdose, fractures, falls, motor vehicle crashes), studies were included with outcomes measured at shorter intervals because such outcomes can occur early during opioid therapy. A detailed listing of the key questions can be found in Online Appendix 1: Clinical Evidence Review, available in the “Supporting Documents” section of the docket.

Clinical Evidence Systematic Review Methods

Complete methods and data for the 2014 AHRQ report, upon which this updated systematic review is based, have been published previously (10,40). Study authors developed the protocol using a standardized process (41) with input from experts and constituents and registered the protocol in the PROSPERO database (42). CDC conducted an updated literature search using the same search strategies as in the original review. Seven additional studies met inclusion criteria and were added to the review. Information about data sources and searches, study selection, data extraction and quality assessment, data synthesis, and update search yield and new evidence for the current review can be found in Online Appendix 1: Clinical Evidence Review, available in the “Supporting Documents” section of the docket.

Summary of Findings for Clinical Questions

The main findings of this updated review are consistent with the findings of the 2014 AHRQ report (10). In summary, evidence on long-term opioid therapy for chronic pain outside of end-of-life care remains limited, with insufficient evidence to determine long-term benefits, though evidence suggests risk for serious harms that appears to be dose-dependent. These findings supplement findings from a previous review of the effectiveness of opioids for adults with chronic noncancer pain. In this previous review, based on randomized trials predominantly <12 weeks in duration, opioids were found to be moderately effective for pain relief, with small benefits for functional outcomes; although estimates vary, based on uncontrolled studies, a high percentage of patients discontinued long-term opioid use because of lack of efficacy and because of adverse events (24).

The GRADE evidence summary with type of evidence ratings for the five clinical questions for the current evidence review are outlined (Table). This summary is based on studies included in the AHRQ 2014 review (35 studies) plus additional studies identified in the updated search (7 studies). Additional details on findings from the original review are available in the full 2014 AHRQ report (10,40). Full details on the clinical evidence review findings supporting this guideline can be found in Online Appendix 1: Clinical Evidence Review, available in the “Supporting Documents” section of the docket.

Effectiveness

For KQ1, no study of opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for chronic pain evaluated long-term (>1 year) outcomes related to pain, function, or quality of life. Most placebo-

controlled randomized trials were ≤ 6 weeks in duration. Thus, the body of evidence for KQ1 is rated as insufficient (0 studies contributing) (10).

Harms

For KQ2, the body of evidence is rated as type 3 (12 studies contributing; 11 from the original review plus 1 new study). One fair-quality cohort study found that long-term opioid therapy is associated with increased risk for an opioid abuse or dependence diagnosis versus no opioid prescription (18). Rates of opioid abuse or dependence ranged from 0.7% with lower-dose (≤ 36 MME) chronic therapy to 6.1% with higher-dose (≥ 120 MME) chronic therapy, versus 0.004% with no opioids. Ten fair-quality uncontrolled studies reported estimates of opioid abuse, addiction, and related outcomes (43–53). In primary care settings, prevalence of opioid dependence (using DSM-IV criteria) ranged from 3% to 26% (43,44,47). In pain clinic settings, prevalence of addiction ranged from 2% to 14% (45,46,48,49,51–53).

Factors associated with increased risk for misuse included history of substance use disorder, younger age, major depression, and use of psychotropic medications (44,50). Two studies reported on the association between opioid use and risk for overdose (54,55). One large fair-quality retrospective cohort study found that recent opioid use was associated with increased risk for any overdose events and serious overdose events versus nonuse (54). It also found higher doses associated with increased risk. Relative to 1–19 MME/day, the adjusted hazard ratio (HR) for any overdose event (consisting of mostly nonfatal overdose) was 1.44 for 20 to 49 MME/day, 3.73 for 50–99 MME/day, and 8.87 for ≥ 100 MME/day. A similar pattern was observed for serious overdose. A good-quality population-based, nested case-control study also found a dose-dependent association with risk for overdose death (55). Relative to 1–19 MME/day, the adjusted odds ratio (OR) was 1.32 for 20–49 MME/day, 1.92 for 50–99 MME/day, 2.04 for 100–199 MME/day, and 2.88 for ≥ 200 MME/day.

Findings of increased fracture risk for current opioid use, versus nonuse, were mixed in two studies (56,57). Two studies found an association between opioid use and increased risk for cardiovascular events (58,59). Indirect evidence was found for endocrinologic harms (increased use of medications for erectile dysfunction or testosterone from one previously included study; laboratory-defined androgen deficiency from one newly reviewed study) (60,61). One study found that opioid dosages ≥ 20 MME/day were associated with increased odds of road trauma among drivers (62).

Opioid Dosing Strategies

For KQ3, the body of evidence is rated as type 4 (14 studies contributing; 12 from the original review plus two new studies). For initiation and titration of opioids, the 2014 AHRQ report found insufficient evidence from three fair-quality, open-label trials to determine comparative effectiveness of ER/LA versus immediate-release opioids for titrating patients to stable pain control (63,64). One new fair-quality cohort study of Veterans Affairs patients found initiation of therapy with an ER/LA opioid associated with greater risk for nonfatal overdose than initiation with an immediate-release opioid, with risk greatest in the first 2 weeks after initiation of treatment (65).

For comparative effectiveness and harms of ER/LA opioids, the 2014 AHRQ report included three randomized, head-to-head trials of various ER/LA opioids that found no clear differences in 1-year outcomes related to pain or function (66–68) but had methodological shortcomings. A fair-quality retrospective cohort study based on national Veterans Health Administration system pharmacy data found that methadone was associated with lower overall risk for all-cause mortality versus morphine (69), and a fair-quality retrospective cohort study based on Oregon Medicaid data found no statistically significant differences between methadone and long-acting morphine in risk for death or overdose symptoms (70). However, a new observational study (71) found methadone associated with increased risk for overdose versus sustained-release morphine among Tennessee Medicaid patients. The observed inconsistency in study findings suggests that risks of methadone might vary in different settings as a

function of different monitoring and management protocols, though more research is needed to understand factors associated with safer methadone prescribing.

For dose escalation, the 2014 AHRQ report included one fair-quality randomized trial that found no differences between more liberal dose escalation and maintenance of current doses after 12 months in pain, function, all-cause withdrawals, or withdrawals due to opioid misuse (72). However, the difference in opioid dosages prescribed at the end of the trial was relatively small (mean 52 MME/day with more liberal dosing versus 40 MME/day). Evidence on other comparisons related to opioid dosing strategies (ER/LA versus immediate-release opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled continuous dosing versus as-needed dosing; or opioid rotation versus maintenance of current therapy; long-term effects of strategies for treating acute exacerbations of chronic pain) was not available or too limited to determine effects on long-term clinical outcomes. For example, evidence on the comparative effectiveness of opioid tapering or discontinuation versus maintenance, and of different opioid tapering strategies, was limited to small, poor-quality studies (73–75).

Risk Assessment and Mitigation

For KQ4, the body of evidence is rated as type 3 for the accuracy of risk assessment tools and insufficient for the effectiveness of use of risk assessment tools and mitigation strategies in reducing harms (six studies contributing; four from the original review plus two new studies). The 2014 AHRQ report included four studies (76–79) on the accuracy of risk assessment instruments, administered prior to opioid therapy initiation, for predicting opioid abuse or misuse. Results for the Opioid Risk Tool (ORT) (77–79) were extremely inconsistent; evidence for other risk assessment instruments was very sparse, and studies had serious methodological shortcomings. One additional fair-quality (80) and one poor-quality (81) study identified for this update compared the predictive accuracy of the ORT, the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R), and the Brief Risk Interview. For the ORT, sensitivity was 0.58 and 0.75 and specificity 0.54 and 0.86; for the SOAPP-R, sensitivity was 0.53 and 0.25 and specificity 0.62 and 0.73; and for the Brief Risk Interview, sensitivity was 0.73 and 0.83 and specificity 0.43 and 0.88. For the ORT, positive likelihood ratios ranged from noninformative (positive likelihood ratio close to 1) to moderately useful (positive likelihood ratio >5). The SOAPP-R was associated with noninformative likelihood ratios (estimates close to 1) in both studies.

No study evaluated the effectiveness of risk mitigation strategies (use of risk assessment instruments, opioid management plans, patient education, urine drug testing, use of PDMP data, use of monitoring instruments, more frequent monitoring intervals, pill counts, or use of abuse-deterrent formulations) for improving outcomes related to overdose, addiction, abuse, or misuse.

Effects of Opioid Therapy for Acute Pain on Long-Term Use

For KQ5, the body of evidence is rated as type 3 (two new studies contributing). Two fair-quality retrospective cohort studies found opioid therapy prescribed for acute pain associated with greater likelihood of long-term use. One study evaluated opioid-naïve patients who had undergone low-risk surgery, such as cataract surgery and varicose vein stripping (82). Use of opioids within 7 days of surgery was associated with increased risk for use at 1 year. The other study found that among patients with a workers' compensation claim for acute low back pain, compared to patients who did not receive opioids early after injury (defined as use within 15 days following onset of pain), patients who did receive early opioids had an increased likelihood of receiving five or more opioid prescriptions 30 to 730 days following onset that increased with greater early exposure (83).

Contextual Evidence Review

Primary Areas of Focus

Contextual evidence is complementary information that assists in translating the clinical research findings into recommendations. CDC conducted contextual evidence reviews on four topics to supplement the clinical evidence review findings:

- Effectiveness of alternative treatments, including nonpharmacologic (e.g., cognitive behavioral therapy [CBT], exercise therapy, interventional treatments, and multimodal pain treatment) and nonopioid pharmacologic treatments (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], antidepressants, and anticonvulsants), including studies of any duration.
- Benefits and harms of opioid therapy, including findings from the epidemiology and public health literature (rather than the clinical trial literature included in the clinical evidence review) related to specific opioids, high-dose therapy, co-prescription with other controlled substances, duration of use, special populations, and potential usefulness of risk stratification/mitigation approaches, in addition to effectiveness of treatments associated with addressing potential harms of opioid therapy (opioid use disorder).
- Provider and patient values and preferences related to opioids and medication risks, benefits, and use.
- Resource allocation including costs and economic efficiency of opioid therapy and risk mitigation strategies.

CDC also reviewed clinical guidelines that were relevant to opioid prescribing and could inform or complement the CDC recommendations under development (e.g., guidelines on alternative treatments and guidelines with recommendations related to specific provider actions such as urine drug testing or opioid tapering protocols).

Contextual Evidence Review Methods

Given the public health urgency for developing opioid prescribing recommendations, a rapid review was required for the contextual evidence review for the current guideline. Rapid reviews are used when there is a need to streamline the systematic review process to obtain evidence quickly (84). Methods used to streamline the process include limiting searches by databases, years, and languages considered, and truncating quality assessment and data abstraction protocols. CDC conducted “rapid reviews” of the contextual evidence on alternative treatments, benefits and harms, values and preferences, and resource allocation.

Detailed information about contextual evidence data sources and searches, inclusion criteria, study selection, and data extraction and synthesis are available in Online Appendix 2: Contextual Evidence Review, available in the “Supporting Documents” section of the docket. In brief, CDC conducted systematic literature searches to identify original studies, systematic reviews, and clinical guidelines, depending on the topic being searched. CDC also solicited publication referrals from subject matter experts. Given the need for a rapid review process, grey literature (e.g., literature by academia, organizations, or government in the forms of reports, documents, or proceedings not published by commercial publishers) was not systematically searched. Database sources, including MEDLINE, PsycINFO, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, varied by topic. Multiple reviewers scanned study abstracts identified through the database searches and extracted relevant studies for review. CDC constructed narrative summaries and tables based on relevant articles that met inclusion criteria (see Online Appendix 2 for criteria).

Findings from the contextual reviews provide indirect evidence and should be interpreted accordingly. CDC did not formally rate the quality of evidence for the studies included in the contextual evidence review using the GRADE method. The studies that addressed benefits and harms, values and preferences, and resource allocation most often employed observational methods, used short follow-up periods, and evaluated selected samples. Therefore the strength of the evidence from these contextual review areas was considered to be low, comparable to type 3 or type 4 evidence. The quality of evidence for nonopioid pharmacologic and nonpharmacologic pain treatments was generally rated as moderate, comparable to type 2 evidence, in systematic reviews and clinical guidelines (e.g., for treatment of chronic neuropathic pain, low back pain, osteoarthritis, and fibromyalgia). Similarly, the quality of evidence on pharmacologic and psychosocial opioid use disorder treatment was generally rated as moderate, comparable to type 2 evidence, in systematic reviews and clinical guidelines.

Summary of Findings for Contextual Areas

Full narrative reviews and tables that summarize key findings from the contextual evidence review are provided in Online Appendix 2: Contextual Evidence Review, available in the “Supporting Documents” section of the docket.

Effectiveness of Alternative Treatments

Several nonpharmacologic and nonopioid pharmacologic treatments have been shown to be effective in managing chronic pain in studies ranging in duration from 2 weeks to 6 months. For example, CBT that trains patients in behavioral techniques and helps patients modify situational factors and cognitive processes that exacerbate pain has small positive effects on disability and catastrophic thinking (85). Exercise therapy can help reduce pain and improve function in chronic low back pain (86), improve function and reduce pain in osteoarthritis of the knee (87) and hip (88), and improve well-being, fibromyalgia symptoms, and physical function in fibromyalgia (89). Multimodal and multidisciplinary therapies (e.g., therapies that combine exercise and related therapies with psychologically based approaches) can help reduce pain and improve function more effectively than single modalities (90,91). Nonopioid pharmacologic approaches used for pain include analgesics such as acetaminophen, NSAIDs, and cyclooxygenase 2 (COX-2) inhibitors; selected anticonvulsants; and selected antidepressants (particularly tricyclics and serotonin and norepinephrine reuptake inhibitors [SNRIs]). Multiple guidelines recommend acetaminophen as first-line pharmacotherapy for osteoarthritis (92–97) or for low back pain (98) but note that it should be avoided in liver failure and that dosage should be reduced in patients with hepatic insufficiency or a history of alcohol abuse (97). Although guidelines also recommend NSAIDs as first-line treatment for osteoarthritis or low back pain (94,98), NSAIDs and COX-2 inhibitors do have risks, including gastrointestinal bleeding or perforation as well as renal and cardiovascular risks (99). FDA has recently strengthened existing label warnings that NSAIDs increase risks for heart attack and stroke, including that these risks might increase with longer use or at higher doses (100). Several guidelines agree that first- and second-line drugs for neuropathic pain include anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, and SNRIs (101–104). Interventional approaches such as epidural injection for certain conditions (e.g., lumbar radiculopathy) can provide short-term improvement in pain and in function that can facilitate exercise therapy (105–107). However, evidence has not demonstrated long-term benefit, and epidural injection has been associated with rare but serious adverse events, including loss of vision, stroke, paralysis, and death (108).

Benefits and Harms of Opioid Therapy

Balance between benefits and harms is a critical factor influencing the strength of clinical recommendations. In particular, CDC considered what is known from the epidemiology research about benefits and harms related to specific opioids and formulations, high dose therapy, co-prescription with

other controlled substances, duration of use, special populations, and risk stratification and mitigation approaches. Additional information on benefits and harms of long-term opioid therapy from studies meeting rigorous selection criteria can be found in the clinical evidence review (e.g., see KQ2). CDC also considered the number of persons experiencing chronic pain, numbers potentially benefiting from opioids, and numbers affected by opioid-related harms. A review of these data is presented in the background section of this document, with detailed information presented available in Online Appendix 2: Contextual Evidence Review, available in the “Supporting Documents” section of the docket. Finally, CDC considered the effectiveness of treatments that addressed potential harms of opioid therapy (opioid use disorder).

Regarding specific opioids and formulations, as noted by FDA, there are serious risks of ER/LA opioids, and the indication for this class of medications is for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment in patients for whom alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain (109). Time-scheduled opioid use was associated with substantially higher average daily opioid dosage than as-needed opioid use in one study (110). Methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for pain. Methadone has been found to account for as much as a third of opioid-related overdose deaths involving single or multiple drugs in states that participated in the Drug Abuse Warning Network, which was more than any opioid other than oxycodone, despite representing <2% of opioid prescriptions outside of opioid treatment programs in the United States; further, methadone was involved in twice as many single-drug deaths as any other prescription opioid (111).

Regarding high-dose therapy, several epidemiologic studies that were excluded from the clinical evidence review because patient samples were not restricted to patients with chronic pain also examined the association between opioid dosage and overdose risk (19,20,112–114). Consistent with the clinical evidence review, the contextual review found that opioid-related overdose risk is dose-dependent, with higher opioid dosages associated with increased overdose risk. Two of these studies (19,20), as well as the two studies in the clinical evidence review (115,116), evaluated similar MME/day dose ranges for association with overdose risk. In these four studies, compared with opioids prescribed at <20 MME/day, the odds of overdose among patients prescribed opioids for chronic nonmalignant pain were between 1.3 (116) and 1.9 (20) for dosages of 20 to <50 MME/day, between 1.9 (116) and 4.6 (20) for dosages of 50 to <100 MME/day, and between 2.0 (116) and 8.9 (115) for dosages of ≥100 MME/day. A recent study of Veterans Health Administration patients with chronic pain found that patients who died of overdoses related to opioids were prescribed higher opioid dosages (mean: 98 MME/day; median: 60 MME/day) than controls (mean: 48 MME/day, median: 25 MME/day) (Amy Bohnert, unpublished data, 2015). Finally, another recent study of overdose deaths among state residents with and without opioid prescriptions revealed that prescription opioid-related overdose mortality rates rose rapidly up to prescribed doses of 200 MME/day, after which the mortality rates continued to increase but grew more gradually (117).

Regarding co-prescription of opioids with benzodiazepines, epidemiologic studies suggest that concurrent use of benzodiazepines and opioids might put patients at greater risk for potentially fatal overdose. Three studies of fatal overdose deaths found evidence of concurrent benzodiazepine use in 31%–61% of decedents (116–118). In one of these studies (118), among decedents who received an opioid prescription, those whose deaths were related to opioids were more likely to have obtained opioids from multiple physicians and pharmacies than decedents whose deaths were not related to opioids.

Regarding duration of use, patients can experience tolerance and loss of effectiveness of opioids over time (119). Patients who do not experience clinically meaningful pain relief early in treatment (i.e., within 1 month) are unlikely to experience pain relief with longer-term use (120).

Regarding populations potentially at greater risk for harm, risk is greater for patients with sleep apnea or other causes of sleep-disordered breathing, patients with renal or hepatic insufficiency, older adults, pregnant women, patients with depression or other mental health conditions, and patients with alcohol or other substance use disorders. Interpretation of clinical data on the effects of opioids on sleep-disordered breathing is difficult because of the types of study designs and methods employed, and there is no clear consensus regarding association with risk for developing obstructive sleep apnea syndrome (121). However, opioid therapy can decrease respiratory drive, a high percentage of patients on long-term opioid therapy have been reported to have an abnormal apnea-hypopnea index (122), opioid therapy can worsen central sleep apnea in obstructive sleep apnea patients, and it can cause further desaturation in obstructive sleep apnea patients not on continuous positive airway pressure (CPAP) (25). Reduced renal or hepatic function can result in greater peak effect and longer duration of action and reduce the dose at which respiratory depression and overdose occurs (123). Age-related changes in patients aged ≥ 65 years, such as reduced renal function and medication clearance, even in the absence of renal disease (124), result in a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose. Older adults might also be at increased risk for falls and fractures related to opioids (125–127). Opioids used in pregnancy can be associated with additional risks to both mother and fetus. Opioid treatment during pregnancy has been found to be associated with birth defects, including neural tube defects (128,129), congenital heart defects (129), and gastroschisis (129); preterm delivery (130), poor fetal growth (130), stillbirth (130), and neonatal opioid withdrawal syndrome (131). Patients with mental health comorbidities and patients with histories of substance use disorders might be at higher risk than other patients for opioid use disorder (132–134). Recent analyses found that depressed patients were at higher risk for drug overdose than patients without depression, particularly at higher opioid dosages, although investigators were unable to distinguish unintentional overdose from suicide attempts (135). In case-control and case-cohort studies, substance abuse/dependence was more prevalent among patients experiencing overdose than among patients not experiencing overdose (12% versus 6% [115], 40% versus 10% [20], and 26% versus 9% [19]).

Regarding risk stratification approaches, limited evidence was found regarding benefits and harms. Potential benefits of PDMPs and urine drug testing include the ability to identify patients who might be at higher risk for opioid overdose or opioid use disorder, and help determine which patients will benefit from greater caution and increased monitoring or interventions when risk factors are present. For example, one study found that most fatal overdoses could be retrospectively identified based on two pieces of information (multiple prescribers and high total daily opioid dosage, both important risk factors for overdose [112,136]) that are available to prescribers in the PDMP (112). However, limited evaluation of PDMPs at the state level has revealed mixed effects on changes in prescribing and mortality outcomes (23). Potential harms of risk stratification include underestimation of risks of opioid therapy when screening tools are not adequately sensitive, as well as potential overestimation of risk, which could lead to inappropriate clinical decisions.

Regarding risk mitigation approaches, limited evidence was found regarding benefits and harms. Although no studies were found to examine prescribing of naloxone with opioid pain medication in primary care settings, naloxone distribution through community-based programs providing prevention services for substance users has been demonstrated to be associated with decreased risk for opioid overdose death at the community level (137).

Concerns have been raised that prescribing changes such as dose reduction might be associated with unintended negative consequences, such as patients seeking heroin or other illicitly obtained opioids

(138) or interference with appropriate pain treatment (139). With the exception of a study noting an association between an abuse-deterrent formulation of OxyContin and heroin use, showing that some patients in qualitative interviews reported switching to another opioid, including heroin, for many reasons, including cost and availability as well as ease of use (140), CDC did not identify studies evaluating these potential outcomes.

Finally, regarding the effectiveness of opioid use disorder treatments, methadone and buprenorphine for opioid dependence have been found to increase retention in treatment and to decrease illicit opioid use among patients with opioid dependence involving heroin, particularly when psychosocial treatments (e.g., contingency management, community reinforcement, psychotherapeutic counseling, and family therapy) are used in conjunction with medication-assisted therapy (141–144).

Provider and Patient Values and Preferences

Provider and patient values and preferences can inform how benefits and harms of long-term opioid therapy are weighted and estimate the effort and resources required to effectively provide implementation support. Many physicians lack confidence in their ability to prescribe opioids safely (145), to predict (146) or detect (147) prescription drug abuse, and to discuss abuse with their patients (147). Although providers have reported favorable beliefs and attitudes about improvements in pain and quality of life attributed to opioids (148), most consider prescription drug abuse to be a “moderate” or “big” problem in their community, and large proportions are “very” concerned about opioid addiction (55%) and death (48%) (149). Majorities of providers have reported adverse events including tolerance (62%) and physical dependence (56%) occurring often among patients (149). Providers do not consistently use practices intended to decrease the risk for misuse, such as PDMPs (150,151), urine drug testing (152), and opioid treatment agreements (153). This is likely due in part to challenges related to registering for PDMP access and logging into the PDMP (which can interrupt normal clinical workflow if data are not integrated into electronic health record systems) (154), competing clinical demands, perceived inadequate time to discuss the rationale for urine drug testing and to order confirmatory testing, and feeling unprepared to interpret and address results (155).

Many patients do not have an opinion about “opioids” or know what this term means (156). Most are familiar with the term “narcotics.” About a third associated “narcotics” with addiction or abuse, and about half feared “addiction” from long-term “narcotic” use (156). Most patients taking opioids experience side effects (73% of patients taking hydrocodone for noncancer pain [157], 96% of patients taking opioids for chronic pain [158]), and side effects, rather than pain relief, have been found to explain most of the variation in patients’ preferences related to taking opioids (158). For example, patients taking hydrocodone for noncancer pain commonly reported side effects including dizziness, headache, fatigue, drowsiness, nausea, vomiting, and constipation (157). Patients with chronic pain in focus groups emphasized effectiveness of goal setting for increasing motivation and functioning (159). Patients taking high dosages report reliance on opioids despite ambivalence about their benefits (160) and regardless of pain reduction, reported problems, concerns, side effects, or perceived helpfulness (161).

Resource Allocation

Resource allocation (cost) is an important consideration in understanding the feasibility of clinical recommendations. CDC searched for evidence on opioid therapy compared with alternative treatments; costs of misuse, abuse, and overdose from prescription opioids; and costs of specific risk mitigation strategies (e.g., urine drug testing). Yearly direct and indirect costs related to prescription opioids have been estimated (based on studies published since 2010) to be \$53.4 billion for nonmedical use of prescription opioids (162); \$55.7 billion for abuse, dependence, and misuse of prescription opioids (163); and \$20.4 billion for direct and indirect costs related to opioid-related overdose alone (164). In 2012, total expenses for outpatient prescription opioids were estimated at \$9.0 billion, an increase of 120%

from 2002 (165). Although there are perceptions that opioid therapy for chronic pain is less expensive than more time-intensive nonpharmacologic management approaches, many pain treatments, including acetaminophen, NSAIDs, tricyclic antidepressants, and massage therapy, are associated with lower mean and median annual costs compared with opioid therapy (166). COX-2 inhibitors, SNRIs, anticonvulsants, topical analgesics, physical therapy, and CBT are also associated with lower median annual costs compared with opioid therapy (166). Limited information was found on costs of strategies to decrease risks associated with opioid therapy; however, urine drug testing, including screening and confirmatory tests, has been estimated to cost \$211–\$363 per test (167).

Recommendations

The recommendations are grouped into three areas for consideration:

- Determining when to initiate or continue opioids for chronic pain.
- Opioid selection, dosage, duration, follow-up, and discontinuation.
- Assessing risk and addressing harms of opioid use.

There are 12 recommendations (Box 1). Each recommendation is followed by a rationale for the recommendation, with considerations for implementation noted. In accordance with the ACIP GRADE process, CDC based the recommendations on consideration of the clinical evidence, contextual evidence (including benefits and harms, values and preferences, resource allocation), and expert opinion. For each recommendation statement, CDC notes the recommendation category (A or B) and the type of the evidence (1, 2, 3, or 4) supporting the statement (Box 2). Experts from the Core Expert Group (“experts”) expressed overall support for all recommendations, as well as for the indicated category of the recommendations. Where differences in expert opinion emerged for detailed actions within the clinical recommendations or for implementation considerations, CDC notes the differences of opinion in the supporting rationale statements.

Category A recommendations indicate that most patients should receive the recommended course of action; category B recommendations indicate that different choices will be appropriate for different patients, requiring providers to help patients arrive at a decision consistent with patient values and preferences and specific clinical situations. Consistent with the ACIP (35) and GRADE process (38), category A recommendations were made, even with type 3 and 4 evidence, when there was broad agreement that the advantages of a clinical action greatly outweighed the disadvantages based on a consideration of benefits and harms, values and preferences, and resource allocation. Category B recommendations were made when there was broad agreement that the advantages and disadvantages of a clinical action were more balanced, but advantages were significant enough to warrant a recommendation. All recommendations are category A recommendations, with the exception of recommendation 10, which is rated as category B. Recommendations were associated with a range of evidence types, from type 3 to type 4.

In summary, the categorization of recommendations was based on the following assessment:

- No evidence shows a long-term benefit of opioids in pain and function for chronic pain with outcomes examined at least 1 year later (with most placebo-controlled randomized trials ≤ 6 weeks in duration).
- Extensive evidence shows the possible harms of opioids (including abuse and dependence, overdose, myocardial infarction, motor vehicle crashes).
- Extensive evidence suggests benefits of alternative treatments compared with long-term opioid therapy, including nonpharmacologic therapy and nonopioid pharmacologic therapy, with less harm.

Determining When to Initiate or Continue Opioids for Chronic Pain

- 1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Providers should only consider adding opioid therapy if expected benefits for both pain and function are anticipated to outweigh risks to the patient (recommendation category: A, evidence type 3).**

Patients with pain should receive treatment that provides the greatest benefits relative to risks. Although opioids can reduce pain during short-term use, effects appear relatively small. The clinical evidence review found insufficient evidence to determine whether pain relief is sustained and whether function or quality of life improves with long-term opioid therapy (that is, use of opioids on most days for >3 months) (KQ1). Evidence is limited or insufficient for improved pain or function with long-term use of opioids for several chronic pain conditions for which opioids are commonly prescribed, such as low back pain (168), headache (169), and fibromyalgia (170). While benefits for pain relief, function, and quality of life with long-term opioid use for chronic pain are uncertain, risks associated with long-term opioid use are clearer and significant. Based on the clinical evidence review, long-term opioid use for chronic pain is associated with serious risks including increased risk for abuse and dependence, overdose, myocardial infarction, and motor vehicle crashes (KQ2). At a population level, more than 16,000 persons in the United States die every year from opioid pain-medication-related overdoses (contextual evidence review).

Based on contextual evidence, many nonpharmacologic therapies, including physical therapy, weight loss for knee osteoarthritis, complementary and alternative therapies (e.g., manipulation, massage, and acupuncture), psychological therapies such as CBT, and certain interventional procedures can ameliorate chronic pain. In particular, there is high-quality evidence that exercise therapy (a prominent modality in physical therapy) for hip (88) or knee (87) osteoarthritis reduces pain and improves function immediately after treatment and that the improvements are sustained for at least 2–6 months. Exercise therapy also can help reduce pain and improve function in low back pain and can improve global well-being and physical function in fibromyalgia (86,89). CBT is an activating therapy that addresses psychosocial contributors to pain and improves function (85). Despite this, these therapies are not always or fully covered by insurance, and cost can be a barrier for patients. Multimodal therapies and multidisciplinary biopsychosocial rehabilitation-combining approaches (e.g., psychological therapies with exercise) can reduce long-term pain and disability compared with usual care and compared with physical treatments (e.g., exercise) alone. Multimodal therapies are not always available or reimbursed by insurance and can be time-consuming and costly for patients. Multimodal therapies might therefore be most helpful in patients not responding to single-modality therapy, and combinations should be tailored depending on patient needs, cost, and convenience. Interventional approaches such as arthrocentesis and intraarticular glucocorticoid injection for pain associated with rheumatoid arthritis (105) or osteoarthritis (106) and subacromial corticosteroid injection for rotator cuff disease (107) can provide short-term improvement in pain and function and can facilitate exercise therapy. However, long-term benefit has not been demonstrated, and evidence is insufficient to determine the extent to which repeated injection increases potential risks such as articular cartilage changes (in osteoarthritis) and sepsis (106). Epidural injection has been associated with rare but serious adverse events (108).

Several nonopioid pharmacologic therapies (including acetaminophen, NSAIDs, and selected antidepressants and anticonvulsants) are effective for chronic pain. In particular, acetaminophen and NSAIDs can be useful for arthritis and low back pain. Selected anticonvulsants such as pregabalin and gabapentin can improve pain in diabetic neuropathy, post-herpetic neuralgia, and fibromyalgia (contextual evidence review). Pregabalin, gabapentin, and carbamazepine are FDA-approved for treatment of certain neuropathic pain conditions, and pregabalin is FDA approved for fibromyalgia management. In patients with or without depression, tricyclic antidepressants and SNRIs provide effective analgesia for neuropathic pain conditions including diabetic neuropathy and post-herpetic

neuralgia, often at lower dosages and with a shorter time to onset of effect than for treatment of depression (see contextual evidence review). Tricyclics and SNRIs can also relieve fibromyalgia symptoms. The SNRI duloxetine is FDA-approved for the treatment of diabetic neuropathy and fibromyalgia. Because patients with chronic pain often suffer from concurrent depression (133), and depression can exacerbate physical symptoms including pain (171), patients with co-occurring pain and depression are especially likely to benefit from antidepressant medication (see Recommendation 8).

Nonopioid pharmacologic therapies are not generally associated with drug dependence, and the numbers of fatal overdoses associated with nonopioid medications are a fraction of those associated with opioid medications (contextual evidence review). However, nonopioid pharmacologic therapies are associated with risks, particularly in older patients, pregnant patients, and patients with certain co-morbidities such as cardiovascular, renal, gastrointestinal, and liver disease (see contextual evidence review) and should be used only after assessment and determination that expected benefits outweigh these risks.

Given uncertain benefits and substantial risks, experts agreed that opioids should not be considered first-line or routine therapy for chronic pain (i.e., pain continuing or expected to continue longer than 3 months or past the time of normal tissue healing) outside of active cancer, palliative, and end-of-life care. Nonpharmacologic therapy such as exercise therapy and CBT should be used to reduce pain and improve function in patients with chronic pain. Nonopioid pharmacologic therapy should be used when benefits outweigh risks and should be combined with nonpharmacologic therapy to reduce pain and improve function. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate, to provide greater benefits to patients in improving pain and function.

- 2. Before starting opioid therapy for chronic pain, providers should establish treatment goals with all patients, including realistic goals for pain and function. Providers should not initiate opioid therapy without consideration of how therapy will be discontinued if unsuccessful. Providers should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety (recommendation category: A, evidence type: 4).**

The clinical evidence review found insufficient evidence to determine long-term benefits of opioid therapy for chronic pain and found an increased risk for serious harms related to long-term opioid therapy that appears to be dose-dependent. In addition, studies on currently available risk assessment instruments were sparse and showed inconsistent results (KQ4). The clinical evidence review for the current guideline considered studies with outcomes examined at ≥ 1 year that compared opioid use versus nonuse or placebo. Studies of opioid therapy for chronic pain that did not have a nonopioid control group have found that although many patients discontinue opioid therapy for chronic noncancer pain due to adverse effects or insufficient pain relief, there is weak evidence that patients who are able to continue opioid therapy for at least 6 months can experience clinically significant pain relief and insufficient evidence that function or quality of life improves (172). These findings suggest that it is very difficult for providers to predict whether benefits of opioids for chronic pain will outweigh risks of ongoing treatment for individual patients. Opioid therapy should not be initiated without consideration of an “exit strategy” to be used if the therapy is unsuccessful.

Experts agreed that before opioid therapy is initiated for chronic pain outside of active cancer, palliative, and end-of-life care, providers should determine how effectiveness will be evaluated and should establish treatment goals with patients. Because the line between acute pain and initial chronic pain is not always clear, it might be difficult for providers to determine when they are initiating opioids for chronic pain rather than treating acute pain. Pain lasting longer than 3 months or past the time of normal tissue healing (which could be significantly shorter than 3 months, depending on the condition) is generally no longer considered acute. However, establishing treatment goals with a patient who has already received opioid therapy for 3 months would defer this discussion well past the point of initiation

of opioid therapy for chronic pain. Providers often write prescriptions for long-term use in 30-day increments, and opioid prescriptions written for ≥ 30 days are likely to represent initiation or continuation of long-term opioid therapy. Prior to writing an opioid prescription for ≥ 30 days, providers should establish treatment goals with patients. Providers seeing new patients already receiving opioids should establish treatment goals for continued opioid therapy. Although the clinical evidence review did not find studies evaluating the effectiveness of written agreements or treatment plans (KQ4), providers and patients who set a plan in advance will clarify expectations regarding how opioids will be prescribed and monitored, as well as situations in which opioids will be discontinued or doses tapered (e.g., if treatment goals are not met, opioids are no longer needed, or adverse events put the patient at risk) to improve patient safety.

Experts thought that goals should include improvement in both pain relief and function (and therefore in quality of life). However, there are some clinical circumstances under which reductions in pain without improvement in function might be a more realistic goal (e.g., diseases typically associated with progressive functional impairment or catastrophic injuries such as spinal cord trauma). Experts agreed that providers may use validated instruments such as the three-item “Pain average, interference with Enjoyment of life, and interference with General activity” (PEG) Assessment Scale (173) to track patient outcomes. Clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function (174). Monitoring progress toward patient-centered functional goals (e.g., walking the dog or walking around the block, returning to part-time work, attending family sports or recreational activities) can also contribute to the assessment of functional improvement. Providers should use these goals in assessing benefits of opioid therapy for individual patients and in weighing benefits against risks of continued opioid therapy (see Recommendation 7, including recommended intervals for follow-up). If patients receiving opioid therapy for chronic pain do not experience meaningful improvements in both pain and function compared with prior to initiation of opioid therapy, providers should consider working with patients to taper and discontinue opioids (see Recommendation 7) and should use nonpharmacologic and nonopioid pharmacologic approaches to pain management (see Recommendation 1).

3. Before starting and periodically during opioid therapy, providers should discuss with patients known risks and realistic benefits of opioid therapy and patient and provider responsibilities for managing therapy (recommendation category: A, evidence type: 3).

The clinical evidence review did not find studies evaluating effectiveness of patient education or opioid treatment plans as risk-mitigation strategies (KQ4). However, the contextual evidence review found that many patients lack information about opioids and identified concerns that some providers miss opportunities to effectively communicate about safety (e.g., when unexpected results are found in PDMP information or on urine drug testing). Given the substantial evidence gaps on opioids, uncertain benefits of long-term use, and potential for serious harms, patient education and discussion before starting opioid therapy are critical so that patient preferences and values can be understood and used to inform clinical decisions. Experts agreed that essential elements to communicate to patients before starting and periodically during opioid therapy include realistic expected benefits, common and serious harms, and expectations for provider and patient responsibilities to mitigate risks of opioid therapy.

Providers should involve patients in decisions about whether to start or continue opioid therapy. Given potentially serious risks of long-term opioid therapy, providers should ensure that patients are aware of potential benefits of, harms of, and alternatives to opioids before starting or continuing opioid therapy. Providers should do the following:

- Be explicit and realistic about expected benefits of opioids, explaining that while opioids can reduce pain during short-term use, there is no good evidence that opioids improve

pain or function with long-term use, and that complete relief of pain is unlikely (clinical evidence review, KQ1).

- Emphasize improvement in function as a primary goal and that function can improve even when pain is still present.
- Advise patients about serious adverse effects of opioids, including potentially fatal overdose and development of a potentially serious lifelong opioid use disorder that can cause distress and inability to fulfill major role obligations.
- Advise patients about common adverse effects of opioids, such as constipation, dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms when stopping opioids. To prevent constipation associated with opioid use, advise patients to increase hydration and fiber intake and to maintain or increase physical activity. Stool softeners or laxatives might be needed.
- Discuss increased risks for opioid use disorder, overdose, and death at higher dosages, along with the importance of taking only the amount of opioids prescribed, i.e., not taking more opioids or taking them more often.
- Review increased risks for overdose when opioids are taken with benzodiazepines, other sedatives, alcohol, illicit drugs such as heroin, or other opioids.
- Discuss the importance of periodic reassessment to ensure that opioids are helping to meet patient goals and to allow opportunities for opioid discontinuation and consideration of alternative treatment options if opioids are not effective or are harmful.
- Discuss planned use of precautions to reduce risks, including use of prescription drug monitoring program information (see Recommendation 9) and urine drug testing (see Recommendation 10). Consider including discussion of naloxone use for overdose reversal (see Recommendation 8).
- Consider whether cognitive limitations might interfere with management of opioid therapy (for older adults in particular) and, if so, determine whether a caregiver can responsibly co-manage medication therapy. The importance of reassessing safer medication use should be discussed with both the patient and caregiver.
- Discuss risks to family members and persons in the community if opioids are intentionally or unintentionally shared with others for whom they are not prescribed, including the possibility that others might experience overdose at the same or at lower dosage than prescribed for the patient, and that young children are susceptible to unintentional ingestion. Discuss storage of opioids in a secure, preferably locked location and options for safe disposal of unused opioids (175).

Given the possibility that benefits of opioid therapy might diminish or that risks might become more prominent over time, it is important that providers review expected benefits and risks of continued opioid therapy with patients periodically, at least every 3 months (see Recommendation 7).

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

- 4. When starting opioid therapy for chronic pain, providers should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids (recommendation category: A, evidence type: 4).**

ER/LA opioids include methadone, transdermal fentanyl, and extended-release versions of opioids such as oxycodone, oxymorphone, hydrocodone, and morphine. The clinical evidence review found a fair-

quality study showing a higher risk for overdose among patients initiating treatment with ER/LA opioids than among those initiating treatment with immediate-release opioids (65). The clinical evidence review did not find evidence that continuous, time-scheduled use of ER/LA opioids is more effective or safer than intermittent use of immediate-release opioids or that time-scheduled use of ER/LA opioids reduces risks for opioid misuse or addiction (KQ3).

In 2014, the FDA modified the labeling for ER/LA opioid pain medications, noting serious risks and recommending that ER/LA opioids be reserved for “management of pain severe enough to require daily, around-the-clock, long-term opioid treatment” when “alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain” and not used as “as needed” pain relievers (109). FDA has also noted that some ER/LA opioids are only appropriate for opioid-tolerant patients, defined as patients who have received certain dosages of opioids (e.g., 60 mg daily of oral morphine, 30 mg daily of oral oxycodone, or equianalgesic dosages of other opioids) for at least 1 week (176). Time-scheduled opioid use can be associated with greater total average daily opioid dosage compared with intermittent, as-needed opioid use (contextual evidence review). In addition, experts indicated that there was not enough evidence to determine the safety of using immediate-release opioids for breakthrough pain when ER/LA opioids are used for chronic pain outside of active cancer pain, palliative care, or end-of-life care, and that this practice might be associated with dose escalation.

Abuse-deterrent technologies have been employed to prevent manipulation intended to defeat extended-release properties of ER/LA opioids and to prevent opioid use by unintended routes of administration, such as injection of oral opioids. As indicated in FDA guidance for industry on evaluation and labeling of abuse-deterrent opioids (177), although abuse-deterrent technologies are expected to make manipulation of opioids more difficult or less rewarding, they do not prevent opioid abuse through oral intake, the most common route of opioid abuse, and can still be abused by nonoral routes. The “abuse-deterrent” label does not indicate that there is no risk for abuse. No studies were found in the clinical evidence review assessing the effectiveness of abuse-deterrent technologies as a risk mitigation strategy for deterring or preventing abuse. In addition, abuse-deterrent technologies do not prevent unintentional overdose through oral intake. Experts agreed that recommendations could not be offered at this time related to use of abuse-deterrent formulations.

In comparing different ER/LA formulations, the clinical evidence review found inconsistent results for overdose risk with methadone versus other ER/LA opioids used for chronic pain (KQ3). The contextual evidence review found that methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for chronic pain. In addition, methadone is associated with cardiac arrhythmias along with QT prolongation on the electrocardiogram, and it has complicated pharmacokinetics and pharmacodynamics, including a long and variable half-life and peak respiratory depressant effect occurring later and lasting longer than peak analgesic effect. Experts noted that the pharmacodynamics of methadone are subject to more inter-individual variability than other opioids. In regard to other ER/LA opioid formulations, experts noted that the absorption and pharmacodynamics of transdermal fentanyl are complex, with gradually increasing serum concentration during the first part of the 72-hour dosing interval, as well as variable absorption based on factors such as external heat. In addition, the dosing of transdermal fentanyl in mcg/hour, which is not typical for a drug used by outpatients, can be confusing. Experts thought that these complexities might increase the risk for fatal overdose when methadone or transdermal fentanyl is prescribed to a patient who has not used it previously or by providers who are not familiar with its effects.

Experts agreed that for patients not already receiving opioids, providers should not initiate opioid treatment with ER/LA opioids and should not prescribe ER/LA opioids for intermittent use. ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who

have received immediate-release opioids daily for at least 1 week. When changing to an ER/LA opioid for a patient previously receiving a different immediate-release opioid, providers should consult product labeling and reduce total daily dosage to account for incomplete opioid cross-tolerance. Providers should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with renal or hepatic dysfunction because decreased clearance of drugs among these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations. Although there might be situations in which clinicians need to prescribe immediate-release and ER/LA opioids together (e.g., transitioning patients from ER/LA opioids to immediate-release opioids by temporarily using lower dosages of both), in general, avoiding the use of immediate-release opioids in combination with ER/LA opioids is preferable, given potentially increased risk and diminishing returns of such an approach for chronic pain.

When an ER/LA opioid is prescribed, using one with predictable pharmacokinetics and pharmacodynamics is preferred to minimize unintentional overdose risk. In particular, unusual characteristics of methadone and of transdermal fentanyl make safe prescribing of these medications for pain especially challenging.

- Methadone should not be the first choice for an ER/LA opioid. Only providers who are familiar with methadone's unique risk profile and who are prepared to educate and closely monitor their patients, including risk assessment for QT prolongation and consideration of electrocardiographic monitoring, should consider prescribing methadone for pain. A clinical practice guideline that contains further guidance regarding methadone prescribing for pain has been published previously (178).
- Because dosing effects of transdermal fentanyl are often misunderstood by both providers and patients, only providers who are familiar with the dosing and absorption properties of transdermal fentanyl and are prepared to educate their patients about its use should consider prescribing it.

5. When opioids are started, providers should prescribe the lowest effective dosage. Providers should use caution when prescribing opioids at any dosage, should implement additional precautions when increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day, and should generally avoid increasing dosage to ≥ 90 MME/day (recommendation category: A, evidence type: 3).

Benefits of high-dose opioids for chronic pain are not established. The clinical evidence review found only one study (72) addressing effectiveness of dose titration for outcomes related to pain control, function, and quality of life (KQ3). This randomized trial found no difference in pain or function between a more liberal opioid dose escalation strategy and maintenance of current dosage. (These groups were prescribed average dosages of 52 and 40 MME/day, respectively, at the end of the trial.) At the same time, risks for serious harms related to opioid therapy increase at higher opioid dosage. The clinical evidence review found that higher opioid dosages are associated with increased risks for motor vehicle crashes, opioid abuse or dependence, and overdose (KQ2). The clinical and contextual evidence reviews found that opioid overdose risk increases in a dose-response manner, that dosages of 50–99 MME/day have been found to increase risks for opioid overdose by factors of 1.9 to 4.6 compared with dosages of 1–19 MME/day, and that dosages ≥ 100 MME/day are associated with increased risks of overdose 2.0–8.9 times the risk at 1–19 MME/day.

The contextual evidence review found that although there is not a single dosage threshold below which overdose risk is eliminated, holding dosages < 50 MME/day would likely reduce risk among a large proportion of patients who would experience fatal overdose at higher prescribed dosages. Experts agreed that lower dosages of opioids reduce the risk for overdose, but that a single dosage threshold for safe opioid use could not be identified. Experts noted that daily opioid dosages < 50 MME/day are safer than dosages of 50–100 MME/day, and that dosages < 20 MME/day are safer than dosages of 20–50

MME/day. Experts agreed that, in general, increasing dosages to 50 or more MME/day increases overdose risk without necessarily adding benefits for pain control or function. Experts also agreed that additional precautions should be taken when patients are prescribed daily opioid dosages of ≥ 50 MME/day and that opioid dosages generally should not be increased to ≥ 90 MME/day.

When opioids are used for chronic pain outside of active cancer, palliative, and end-of-life care, providers should start opioids at the lowest possible effective dosage (i.e., the lowest starting dosage on product labeling). Providers should use additional caution when initiating opioids for patients aged ≥ 65 years and for patients with renal or hepatic insufficiency because decreased clearance of drugs in these patients can result in accumulation of drugs to toxic levels. Providers should use caution when increasing opioid dosages and increase dosage by the smallest practical amount because overdose risk increases with increases in opioid dosage. Although there is limited evidence to recommend specific intervals for dosage titration, a previous guideline recommended waiting at least five half-lives before increasing dosage and waiting at least a week before increasing dosage of methadone and fentanyl to make sure that full effects of the previous dosage are evident (25). Providers should re-evaluate patients after increasing dosage (see Recommendation 7). If a patient's opioid dosage for all sources of opioids combined reaches or exceeds 50 MME/day, providers should reassess the patient's pain, function, and treatment and should implement additional precautions, including increased frequency of follow-up (see Recommendation 7). Providers should take additional steps to mitigate overdose risk for patients receiving total daily opioid dosages of ≥ 50 MME/day, such as considering offering naloxone and overdose prevention education to both patients and the patients' household members (see Recommendation 8). Providers should generally avoid increasing opioid dosages to ≥ 90 MME/day. If patients do not experience improvement in pain and function at ≥ 90 MME/day, or if there are escalating dosage requirements, providers should discuss other approaches to pain management with the patient, consider working with patients to taper and discontinue opioids (see Recommendation 7), and should consider consulting a pain specialist. Some states require providers to implement clinical protocols at specific dosage levels; providers should be aware of rules related to MME thresholds and associated clinical protocols established by their states.

Established patients already taking high dosages of opioids, as well as patients transferring from other providers, might consider the possibility of opioid dosage reduction to be anxiety-provoking, and tapering opioids can be especially challenging after years on high dosages because of physical and psychological dependence. However, these patients should be offered the opportunity to re-evaluate their continued use of opioids at high dosages in light of recent evidence regarding the association of opioid dosage and overdose risk. Providers should explain in a nonjudgmental manner to patients already taking high opioid dosages (≥ 90 MME/day) that there is now an established body of scientific evidence showing that overdose risk is increased at higher opioid dosages. Providers should empathically review benefits and risks of continued high-dosage opioid therapy and should offer to work with the patient to taper opioids to safer dosages. For patients who agree to taper opioids to lower dosages, providers should collaborate with the patient on a tapering plan (see Recommendation 7). Experts noted that patients tapering opioids after taking them for years might require very slow opioid tapers as well as pauses in the taper to allow gradual accommodation to lower opioid dosages. Providers should remain alert to signs of anxiety, depression, and opioid use disorder (see Recommendations 8 and 12) that might be unmasked by an opioid taper and arrange for management of these co-morbidities. For patients agreeing to taper to lower opioid dosages as well as for those remaining on high opioid dosages, providers should establish goals with the patient for continued opioid therapy (see Recommendation 2), maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 1), and consider consulting a pain specialist as needed to assist with pain management.

6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, providers should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three or fewer days usually will be sufficient for most nontraumatic pain not related to major surgery (recommendation category: A, evidence type: 4).

The clinical evidence review found that opioid use for acute pain (i.e., pain with abrupt onset and caused by an injury or other process that is not ongoing) is associated with long-term opioid use, and that a greater amount of early opioid exposure is associated with greater risk for long-term use (KQ5). Several guidelines on opioid prescribing for acute pain from emergency departments (179–181) and other settings (182,183) have recommended prescribing ≤ 3 days of opioids in most cases, whereas others have recommended < 7 days (184) or < 14 (26) days. Because physical dependence on opioids is an expected physiologic response in patients exposed to opioids for more than a few days (contextual evidence review), limiting days of opioids prescribed also should minimize the need to taper opioids to prevent distressing or unpleasant withdrawal symptoms. Experts noted that more than a few days of exposure to opioids significantly increases hazards and also that prescriptions with fewer days' supply will minimize the number of pills available for unintentional or intentional diversion.

Experts agreed that when opioids are needed for acute pain, providers should prescribe opioids at the lowest effective dose and for no longer than the expected duration of pain severe enough to require opioids to minimize unintentional initiation of long-term opioid use. The lowest effective dose can be determined using product labeling as a starting point with calibration as needed based on the severity of pain and on other clinical factors such as renal or hepatic insufficiency (see Recommendation 8). Experts thought, based on clinical experience regarding anticipated duration of pain severe enough to require an opioid, that in most cases of acute pain not related to major surgery or trauma, a ≤ 3 days' supply of opioids will be sufficient. For example, in one study of the course of acute low back pain (not associated with malignancies, infections, spondylarthropathies, fractures, or neurological signs) in a primary care setting, there was a large decrease in pain until the fourth day after treatment with paracetamol, with smaller decreases thereafter (185). Providers should consider a default of ≤ 3 days of opioids for acute pain and adjust the duration based on the circumstances of the pain syndrome. Providers should not prescribe additional opioids to patients "just in case" pain continues longer than expected. Providers should re-evaluate the subset of patients who experience severe acute pain that continues longer than the expected duration to confirm or revise the initial diagnosis and to adjust management accordingly. Given longer half-lives and longer duration of effects (e.g., respiratory depression) with LA/ER opioids such as methadone, fentanyl patches, or extended release versions of opioids such as oxycodone, oxymorphone, or morphine, providers should not prescribe ER/LA opioids for the treatment of acute pain.

7. Providers should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Providers should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, providers should work with patients to reduce opioid dosage and to discontinue opioids (recommendation category: A, evidence type: 4).

Although the clinical evidence review did not find studies evaluating the effectiveness of more frequent monitoring intervals (KQ4), it did find that continuing opioid therapy for 3 months substantially increases risk for opioid use disorder (KQ2); therefore, follow-up earlier than 3 months might be necessary to provide the greatest opportunity to prevent the development of opioid use disorder. In addition, risk for overdose associated with ER/LA opioids might be particularly high during the first 2 weeks of treatment (KQ3). The contextual evidence review found that patients who do not have pain relief with opioids at 1 month are unlikely to experience pain relief with opioids at 6 months. Although evidence is insufficient to determine at what point within the first 3 months of opioid therapy the risks

for opioid use disorder increase, reassessment of pain and function within 1 month of initiating opioids provides an opportunity to minimize risks of long-term opioid use by discontinuing opioids among patients not receiving a clear benefit from these medications. Experts noted that risks for opioid overdose are greatest during the first 3–7 days after opioid initiation or increase in dosage, particularly when methadone or transdermal fentanyl are prescribed; that follow-up within 3 days is appropriate when initiating or increasing the dosage of methadone; and that follow-up within 1 week might be appropriate when initiating or increasing the dosage of other ER/LA opioids.

Providers should evaluate patients to assess benefits and harms of opioids within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation. Providers should consider follow-up intervals within the lower end of this range when ER/LA opioids are started or increased or when total daily opioid dosage is ≥ 50 MME/day. Shorter follow-up intervals (within 3 days) should be strongly considered when starting or increasing the dosage of methadone. At follow up, providers should assess benefits in function, pain control, and quality of life using tools such as the 3-item “Pain average, interference with Enjoyment of life, and interference with General activity” (PEG) Assessment Scale (173) and/or asking patients about progress toward functional goals that have meaning for them (see Recommendation 2). Providers should also ask patients about common adverse effects such as constipation and drowsiness (see Recommendation 3), as well as asking about and assessing for effects that might be early warning signs for more serious problems such as overdose (e.g., sedation, slurred speech, ataxia) or opioid use disorder (e.g., craving, wanting to take opioids in greater quantities or more frequently than prescribed, difficulty controlling use). Providers should ask patients about their preferences for continuing opioids, given their effects on pain and function relative to any adverse effects experienced.

Because of potential changes in the balance of benefits and risks of opioid therapy over time, providers should regularly reassess all patients receiving long-term opioid therapy at least every 3 months. At reassessment, providers should determine whether opioids continue to meet treatment goals, including sustained improvement in pain and function, whether the patient has experienced common or serious adverse events or early warning signs of serious adverse events, signs of opioid use disorder (e.g., difficulty controlling use, work or family problems related to opioid use), whether benefits of opioids continue to outweigh risks, and whether opioid dosage can be reduced or opioids can be discontinued. Ideally, these reassessments would take place in person and be conducted by the prescribing provider. In practice contexts where virtual visits are part of standard care (e.g., in remote areas where distance or other issues make follow-up visits challenging), follow-up assessments that allow the provider to communicate with and observe the patient through video and audio could be conducted, with in-person visits occurring at least once per year. Providers should re-evaluate patients who are exposed to greater risk (e.g., patients with depression or other mental health conditions, history of substance use disorder, taking ≥ 50 MME/day) more frequently than every 3 months. If clinically meaningful improvements in pain and function are not sustained, if patients are on high-risk regimens (e.g., dosages ≥ 50 MME/day or opioids combined with benzodiazepines) without evidence of benefit, if patients believe benefits no longer outweigh risks or if they request dosage reduction or discontinuation, or if patients experience overdose or other serious adverse events (e.g., an event leading to hospitalization or disability) or warning signs of serious adverse events, providers should work with patients to reduce opioid dosage and to discontinue opioids when possible. Providers should maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 1) and consider consulting a pain specialist as needed to assist with pain management.

Considerations for Tapering Opioids

Although the clinical evidence review did not find high-quality studies comparing the effectiveness of different tapering protocols for use when opioid dosage is reduced or opioids are discontinued (KQ3), tapers reducing weekly dosage by 10%–50% of the original dosage have been recommended by other

clinical guidelines (186), and a rapid taper over 2–3 weeks has been recommended in the case of a severe adverse event such as overdose (26). Experts noted that tapers slower than 10% per week (e.g., 10% per month) might also be appropriate and better tolerated than more rapid tapers, particularly when patients have been taking opioids for longer durations (e.g., for years). Opioid withdrawal during pregnancy has been associated with spontaneous abortion and premature labor.

When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs of opioid withdrawal (e.g., drug craving, anxiety, insomnia, abdominal pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection) should be used. A decrease of 10% of the original dose per week is a reasonable starting point; experts agreed that tapering plans may be individualized based on patient goals and concerns. Experts noted that at times, tapers might have to be paused and restarted again when the patient is ready and might have to be slowed once patients reach low dosages. Tapers may be considered successful as long as the patient is making progress. Once the smallest available dose is reached, the interval between doses can be extended. Opioids may be stopped when taken less frequently than once a day. More rapid tapers might be needed for patient safety under certain circumstances (e.g., for patients who have experienced overdose on their current dosage). Ultrarapid detoxification under anesthesia is associated with substantial risks, including death, and should not be used (187). Providers should access appropriate expertise if considering tapering opioids during pregnancy because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal. Patients who are not taking opioids (including patients who are diverting all opioids they obtain) do not require tapers. Providers should discuss with patients undergoing tapering the increased risk for overdose on abrupt return to a previously prescribed higher dose. Nonopioid pain management (see Recommendation 1), as well as psychosocial support for anxiety related to the taper, should be optimized. More detailed guidance on tapering, including management of withdrawal symptoms has been published previously (26,188). If a patient exhibits signs of opioid use disorder (dependence, addiction), providers should offer or arrange for treatment of opioid use disorder (see Recommendation 12) and consider offering naloxone for overdose prevention (see Recommendation 8).

Assessing Risk and Addressing Harms of Opioid Use

8. Before starting and periodically during continuation of opioid therapy, providers should evaluate risk factors for opioid-related harms. Providers should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, or higher opioid dosages (≥ 50 MME), are present (recommendation category: A, evidence type: 4).

The clinical evidence review found insufficient evidence to determine how harms of opioids differ depending on patient demographics or patient comorbidities (KQ2). However, based on the contextual evidence review and expert opinion, certain risk factors are likely to increase susceptibility to opioid-associated harms and warrant incorporation of additional strategies into the management plan to mitigate risk. Providers should assess these risk factors periodically, with frequency varying by risk factor and patient characteristics. For example, factors that vary more frequently over time, such as alcohol use, require more frequent follow up.

Patients with Sleep-Disordered Breathing, Including Sleep Apnea

Risk factors for sleep-disordered breathing include congestive heart failure, and obesity. Experts noted that careful monitoring and cautious dose titration should be used if opioids are prescribed for patients with mild sleep-disordered breathing. Providers should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing whenever possible to minimize risks for opioid overdose (contextual evidence review).

Pregnant Women

Opioid therapy during pregnancy has been associated with stillbirth, poor fetal growth, pre-term delivery, neonatal opioid withdrawal syndrome, and birth defects (contextual evidence review). Providers and patients should together carefully weigh risks and benefits when making decisions about whether to initiate opioid therapy for chronic pain during pregnancy. In addition, before initiating opioid therapy for chronic pain for reproductive-age women, providers should discuss family planning and how chronic opioid use might affect any future pregnancy. For pregnant women already receiving opioids, providers should access appropriate expertise if considering tapering opioids because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal (see Recommendation 7). For pregnant women with opioid use disorder, medication-assisted therapy with buprenorphine or methadone has been associated with improved maternal outcomes and should be offered (189) (see Recommendation 12). Providers caring for pregnant women receiving opioids for pain or receiving buprenorphine or methadone for opioid use disorder should arrange for delivery at a facility prepared to monitor, evaluate for, and treat neonatal opioid withdrawal syndrome. Neonatal toxicity and death have been reported in breast-feeding infants whose mothers are taking codeine (contextual evidence review); previous guidelines have recommended that codeine be avoided whenever possible among mothers who are breast feeding and, if used, should be limited to the lowest possible dose and to a 4-day supply (190).

Patients with Renal or Hepatic Insufficiency

Providers should use additional caution and increased monitoring (see Recommendation 7) to minimize risks of opioids prescribed for patients with renal or hepatic insufficiency, given their decreased ability to process and excrete drugs, susceptibility to accumulation of opioids, and reduced therapeutic window between safe dosages and dosages associated with respiratory depression and overdose (contextual evidence review; see Recommendations 4, 5, and 7).

Patients Aged ≥ 65 Years

Given reduced renal function and medication clearance even in the absence of renal disease, patients aged ≥ 65 years might have increased susceptibility to accumulation of opioids and a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose (contextual evidence review). Some older adults suffer from cognitive impairment, which can increase risk for medication errors and make opioid-related confusion more dangerous. In addition, older adults are more likely than younger adults to experience co-morbid medical conditions and more likely to receive multiple medications, some of which might interact with opioids (such as benzodiazepines). Providers should use additional caution and increased monitoring (see Recommendations 4, 5, and 7) to minimize risks of opioids prescribed for patients aged ≥ 65 years. Experts suggested that providers educate older adults receiving opioids to avoid risky medication-related behaviors such as obtaining controlled medications from multiple prescribers and saving unused medications. Providers should also implement interventions to mitigate common risks of opioid therapy among older adults, such as exercise or bowel regimens to prevent constipation, risk assessment for falls, and patient monitoring for cognitive impairment.

Patients with Mental Health Conditions

Because psychological distress frequently interferes with improvement of pain and function in patients with chronic pain, using validated instruments such as the Generalized Anxiety Disorder (GAD)-7 and the Patient Health Questionnaire (PHQ)-9 or the PHQ-4 to assess for anxiety, post-traumatic stress disorder, and/or depression (191), might help providers improve overall pain treatment outcomes. Experts noted that providers should use additional caution and increased monitoring (see Recommendation 7) to lessen the increased risk for opioid use disorder among patients with mental health conditions (including depression, anxiety disorders, and PTSD), as well as increased risk for drug overdose among patients with depression. Previous guidelines have noted that opioid therapy should not

be initiated during acute psychiatric instability or uncontrolled suicide risk, and that providers should consider behavioral health specialist consultation for any patient with a history of suicide attempt or psychiatric disorder (25). In addition, patients with anxiety disorders and other mental health conditions are more likely to receive benzodiazepines, which can exacerbate opioid-induced respiratory depression and increase risk for overdose (see Recommendation 11). Providers should ensure that treatment for depression is optimized. Treatment for depression can improve pain symptoms as well as depression and might decrease overdose risk (contextual evidence review). For treatment of chronic pain in patients with depression, providers should strongly consider using tricyclic or SNRI antidepressants for analgesic as well as antidepressant effects if these medications are not otherwise contraindicated (see Recommendation 1).

Patients with Substance Use Disorder

Illicit drugs and alcohol are listed as contributory factors on a substantial proportion of death certificates for opioid-related overdose deaths (contextual evidence review). Previous guidelines have recommended screening or risk assessment tools to identify patients at higher risk for misuse or abuse of opioids. However, the clinical evidence review found that currently available risk-stratification tools (e.g., Opioid Risk Tool, Screener and Opioid Assessment for Patients with Pain Version 1, SOAPP-R, and Brief Risk Interview) show insufficient accuracy for classification of patients as at low risk for abuse or misuse (KQ4). Providers should always exercise caution when considering or prescribing opioids for any patient with chronic pain outside of active cancer, palliative, and end-of-life care and should not overestimate the ability of these tools to rule out risks from long-term opioid therapy.

Providers should ask patients about their drug and alcohol use. Single screening questions can be used (192). For example, the question “How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?” (with an answer of one or more considered positive) was found in a primary care setting to be 100% sensitive and 73.5% specific for the detection of a drug use disorder compared with a standardized diagnostic interview (193). Validated screening tools such as the Drug Abuse Screening Test (DAST) (194) and the Alcohol Use Disorders Identification Test (AUDIT) (195) can also be used. Providers should use PDMP data (see Recommendation 9) and drug testing (see Recommendation 10) as appropriate to assess for concurrent substance use that might place patients at higher risk for opioid use disorder and overdose. Providers should also provide specific counseling on increased risks for overdose when opioids are combined with other drugs or alcohol (see Recommendation 3) and ensure that patients receive effective treatment for substance use disorders when needed (see Recommendation 12).

The clinical evidence review found insufficient evidence to determine how harms of opioids differ depending on past or current substance use disorder (KQ2), although a history of substance use disorder was associated with misuse. Similarly, based on contextual evidence, patients with drug or alcohol use disorders are likely to experience greater risks for opioid abuse and overdose than persons without these conditions. If providers consider opioid therapy for chronic pain outside of active cancer, palliative, and end-of-life care for patients with drug or alcohol use disorders, they should discuss increased risks for opioid use disorder and overdose with patients, carefully consider whether benefits of opioids outweigh increased risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone (see Offering naloxone to patients when factors that increase risk for opioid-related harms are present) and increasing frequency of monitoring (see Recommendation 7) when opioids are prescribed. Because pain management in patients with substance use disorder can be complex, providers should consider consulting substance use disorder specialists and pain specialists regarding pain management for persons with active or recent past history of substance abuse. Experts also noted that providers should communicate with patients’ substance use disorder treatment providers if opioids are prescribed.

Patients with Prior Nonfatal Overdose

Although studies were not identified that directly addressed the risk for overdose among patients with prior nonfatal overdose who are prescribed opioids, based on clinical experience, experts thought that prior nonfatal overdose would substantially increase risk for future nonfatal or fatal opioid overdose. If patients experience nonfatal opioid overdose, providers should work with them to reduce opioid dosage and to discontinue opioids when possible (see Recommendation 7). If providers continue opioid therapy for chronic pain outside of active cancer, palliative, and end-of-life care in patients with prior opioid overdose, they should discuss increased risks for overdose with patients, carefully consider whether benefits of opioids outweigh substantial risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone (see Offering naloxone to patients when factors that increase risk for opioid-related harms are present) and increasing frequency of monitoring (see Recommendation 7) when opioids are prescribed.

Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present

Naloxone is an opioid antagonist that can reverse severe respiratory depression; its administration by lay persons, such as friends and family of persons who experience opioid overdose, can save lives. The contextual evidence review did not find any studies on effectiveness of prescribing naloxone for overdose prevention among patients prescribed opioids for chronic pain. However, there is evidence for effectiveness of naloxone provision in preventing opioid-related overdose death at the community level through community-based distribution (e.g., through overdose education and naloxone distribution programs in community service agencies) to persons at risk for overdose (mostly due to illicit opiate use), and it is plausible that effectiveness would be observed when naloxone is provided in the clinical setting as well. Experts agreed that it is preferable not to initiate opioid treatment when factors that increase risk for opioid-related harms are present. Opinions diverged about the likelihood of naloxone being useful to patients and the circumstances under which it should be offered. However, most experts agreed that providers should consider offering naloxone when prescribing opioids to patients at increased risk for overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients taking benzodiazepines with opioids, patients at risk for returning to a high dose to which they are no longer tolerant (e.g., patients recently released from prison), and patients on higher dosages of opioids (≥ 50 MME/day). Practices should provide education on overdose prevention and naloxone use to patients receiving naloxone prescriptions and to members of their households. Experts noted that naloxone co-prescribing can be facilitated by clinics or practices with resources to provide naloxone training and by collaborative practice models with pharmacists. Resources for prescribing naloxone in primary care settings can be found through Prescribe to Prevent at <http://prescribetoprevent.org>.

9. Providers should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving high opioid dosages or dangerous combinations that put him or her at high risk for overdose. Providers should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months (recommendation category: A, evidence type: 4).

PDMPs are state-based databases that collect information on controlled prescription drugs dispensed by pharmacies in most states and, in select states, by dispensing physicians as well. PDMPs do not currently include information on prescriptions dispensed from Veterans' Health Administration facilities and often do not include prescriptions dispensed in other states. Certain states require providers to review PDMP data prior to writing each opioid prescription (see state-level PDMP-related policies on the National Alliance for Model State Drug Laws website at <http://www.namsdl.org/prescription-monitoring-programs.cfm>). The clinical evidence review did not find studies evaluating the

effectiveness of PDMPs on outcomes related to overdose, addiction, abuse, or misuse (KQ4). However, even though evidence is limited on the effectiveness of PDMP implementation at the state level on prescribing and mortality outcomes (23), the contextual evidence review found that most fatal overdoses were associated with patients receiving opioids from multiple prescribers and/or with patients receiving high total daily opioid dosages; information on both of these risk factors for overdose are available to prescribers in the PDMP. PDMP data can also be helpful when patient medication history is not otherwise available (e.g., for patients from other locales) and when patients transition care to a new provider. The contextual evidence review also found that PDMP information could be used in a way that is harmful to patients. For example, it has been used to dismiss patients from provider practices (196), which might adversely affect patient safety.

The contextual review found variation in state policies that affect timeliness of PDMP data (and therefore benefits of reviewing PDMP data) as well as time and workload for providers in accessing PDMP data. In states that permit delegating access to other members of the health care team, workload for prescribers can be reduced. These differences might result in a different balance of benefits to provider workload in different states. Experts agreed that PDMPs are useful tools that should be consulted when starting a patient on opioid therapy and periodically during long-term opioid therapy. However, experts disagreed on how frequently providers should check the PDMP during long-term opioid therapy, given PDMP access issues and the lag time in reporting in some states. Most experts agreed that PDMP data should be reviewed every 3 months or more frequently during long-term opioid therapy. A minority of experts noted that, given the current burden of accessing PDMP data in some states and the lack of evidence surrounding the most effective interval for PDMP review to improve patient outcomes, annual review of PDMP data during long-term opioid therapy would be reasonable when factors that increase risk for opioid-related harms are not present.

Providers should review PDMP data for opioids and other controlled medications patients might have received from additional prescribers to determine whether a patient is receiving high total opioid dosages or dangerous combinations (e.g., opioids combined with benzodiazepines) that put him or her at high risk for overdose. Ideally, PDMP data should be reviewed before every opioid prescription. This is recommended in all states with well-functioning PDMPs and where PDMP access policies make this practicable (e.g., provider and delegate access permitted), but it is not currently possible in states without functional PDMPs or in those that do not permit certain prescribers to access them. As vendors and practices facilitate integration of PDMP information into regular clinical workflow (e.g., data made available in electronic health records), providers' ease of access in reviewing PDMP data is expected to improve. In addition, improved timeliness of PDMP data will improve their value in identifying patient risks.

If patients are found to have multiple controlled substance prescriptions written by different providers, several actions can be taken to augment providers' abilities to improve patient safety:

- Providers should discuss information from the PDMP with their patient and confirm that the patient is aware of the additional prescriptions. Occasionally, PDMP information can be incorrect (e.g., if a pharmacist entered the wrong name or birthdate, the patient uses a nickname or maiden name, or another person has used the patient's identity to obtain prescriptions).
- Providers should discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving opioids from more than one prescriber or receiving medications that increase risk when combined with opioids (e.g., benzodiazepines) and consider offering naloxone (see Recommendation 8).
- If patients are receiving benzodiazepines, providers should avoid whenever possible prescribing opioids if not yet started or consider tapering opioids if already initiated (see Recommendations

11 and 7). Alternatively, providers and patients can consider tapering benzodiazepines and using alternative therapies for anxiety. Benzodiazepines should be tapered gradually to minimize risks associated with benzodiazepine withdrawal (see Recommendation 11).

- Providers should calculate the total MME/day for concurrent opioid prescriptions to help assess the patient's overdose risk (see Recommendation 5). If patients are found to be receiving high total daily dosages of opioids, providers should discuss their safety concerns with the patient, consider tapering to a safer dosage (see Recommendations 5 and 7), and consider offering naloxone (see Recommendation 8).
- Providers should discuss safety concerns with other providers who are prescribing controlled substances for their patient. Ideally providers should first discuss concerns with their patient and inform him or her that they plan to coordinate care with the patient's other prescribers to improve the patient's safety.
- Providers should consider the possibility of a substance use disorder and discuss concerns with their patient (see Recommendation 12).
- If providers suspect their patient might be sharing or selling opioids and not taking them, providers should consider urine drug testing to assist in determining whether opioids can be discontinued without causing withdrawal (see Recommendations 7 and 10). A negative drug test for prescribed opioids might indicate the patient is not taking prescribed opioids, although providers should consider other possible reasons for this test result (see Recommendation 10).

Experts agreed that providers should not dismiss patients from their practice on the basis of PDMP information. Doing so can adversely affect patient safety, could represent patient abandonment, and could result in missed opportunities to provide potentially lifesaving information (e.g., about risks of opioids and overdose prevention) and interventions (e.g., safer prescriptions, nonopioid pain treatment [see Recommendation 1], naloxone [see Recommendation 8], and effective treatment for substance use disorder [see Recommendation 12]).

10. When prescribing opioids for chronic pain, providers should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs (recommendation category: B, evidence type: 4).

Concurrent use of opioid pain medications with other opioid pain medications, benzodiazepines, or heroin can increase patients' risk for overdose. Urine drug tests can provide information about drug use that is not reported by the patient. In addition, urine drug tests can assist providers in identifying when patients are not taking opioids prescribed for them, which might in some cases indicate diversion or other clinically important issues such as difficulties with adverse effects. Urine drug tests do not provide accurate information about how much or what dose of opioids or other drugs a patient took. The clinical evidence review did not find studies evaluating the effectiveness of urine drug screening for risk mitigation during opioid prescribing for pain (KQ4). The contextual evidence review found that urine drug testing can provide useful information about patients assumed not to be using unreported drugs. Urine drug testing results can be subject to misinterpretation and might sometimes be associated with practices that might harm patients (e.g., stigmatization, inappropriate termination from care). Routine use of urine drug tests with standardized policies at the practice or clinic level might destigmatize their use. Although random drug testing might also destigmatize urine drug testing, experts thought that truly random testing was not feasible in clinical practice. Some clinics obtain a urine specimen every visit, but only send it for testing on a random schedule. Experts noted that in addition to direct costs of urine drug testing, which are often not fully covered by insurance and can be a burden for patients, provider time is needed to interpret, confirm, and communicate results.

Experts agreed that prior to starting opioids for chronic pain and periodically during opioid therapy, providers should use urine drug testing to assess for prescribed opioids as well as other controlled substances and illicit drugs that increase risk for overdose when combined with opioids, including nonprescribed opioids, benzodiazepines, and heroin. While experts agreed that providers should use urine drug testing before initiating opioid therapy for chronic pain, they disagreed on how frequently urine drug testing should be conducted during long-term opioid therapy. Most experts agreed that urine drug testing at least annually for all patients was reasonable. Some experts noted that this interval might be too long in some cases and too short in others, and that the follow-up interval should be left to the discretion of the provider. Previous guidelines have recommended more frequent urine drug testing in patients thought to be at higher risk for substance use disorder. However, experts thought that predicting risk prior to urine drug testing is challenging and that currently available tools do not allow clinicians to reliably identify patients who are at low risk for substance use disorder. Testing of urine is preferred over testing of saliva given that urine drug testing allows for a longer window of detection of drug use (197).

Providers should be familiar with the drugs included in urine drug testing panels used in their practice and should understand how to interpret results for these drugs. For example, a positive “opiates” immunoassay detects morphine, which might reflect patient use of morphine, codeine, or heroin, but this immunoassay does not detect synthetic opioids (e.g., fentanyl, methadone) and might not detect semisynthetic opioids (e.g., oxycodone). However, many laboratories use an oxycodone immunoassay that detects oxycodone and oxymorphone. In some cases, positive results for specific opioids might reflect metabolites from opioids the patient is taking and might not mean the patient is taking the specific opioid for which the test was positive. For example, hydromorphone is a metabolite of hydrocodone, and oxymorphone is a metabolite of oxycodone. Detailed guidance on interpretation of urine drug test results, including which tests to order and expected results, drug detection time in urine, drug metabolism, and other considerations has been published previously (26). Providers should not test for substances for which results would not affect patient management or for which implications for patient management are unclear. For example, experts noted that there might be uncertainty about the clinical implications of a positive urine drug test for tetrahydrocannabinol (THC). Before ordering urine drug testing, providers should have a plan for responding to unexpected results. Providers should explain to patients that urine drug testing is intended to improve their safety and should also explain expected results (e.g., presence of prescribed medication and absence of drugs, including illicit drugs, not reported by the patient). Providers should ask patients about use of prescribed and other drugs and ask whether there might be unexpected results. This will provide an opportunity for patients to provide information about changes in their use of prescribed opioids or other drugs. Providers should discuss unexpected results with the local laboratory or toxicologist and with patients. Discussion with patients prior to specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and obviate the need for expensive confirmatory testing on that visit. If unexpected results are not explained, they should be verified with more specific confirmatory testing that uses gas or liquid chromatography/mass spectrometry.

Providers should use unexpected results to improve patient safety (e.g., change in pain management strategy [see Recommendation 1], tapering or discontinuation of opioids [see Recommendation 7], more frequent re-evaluation [see Recommendation 7], offering naloxone [see Recommendation 8], or referral for treatment for substance use disorder [see Recommendation 12], all as appropriate). Providers should not terminate patients from care based on a urine drug test result because this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including the patient obtaining opioids from alternative sources and the provider missing opportunities to facilitate treatment for substance use disorder.

11. Providers should avoid prescribing opioid pain medication for patients receiving benzodiazepines whenever possible (recommendation category: A, evidence type: 3).

Benzodiazepines and opioids both cause central nervous system depression and can decrease respiratory drive. Concurrent use is likely to put patients at greater risk for potentially fatal overdose. The clinical evidence review did not address risks of benzodiazepine co-prescription among patients prescribed opioids. However, the contextual evidence review found evidence in epidemiologic series of concurrent benzodiazepine use in large proportions of opioid-related overdose deaths, and a case-cohort study found concurrent benzodiazepine prescription with opioid prescription to be associated with a near quadrupling of risk for overdose death compared with opioid prescription alone (198). Experts agreed that although there are circumstances when it might be appropriate to prescribe opioids to a patient receiving benzodiazepines (e.g., severe acute pain in a patient on long-term, stable low-dose benzodiazepine therapy), providers should avoid prescribing opioids for patients receiving benzodiazepines whenever possible. Because of greater risks of benzodiazepine withdrawal relative to opioid withdrawal, and because tapering opioids can be associated with anxiety, when patients receiving both benzodiazepines and opioids require tapering to reduce risk for fatal respiratory depression, it might be safer and more practical to taper opioids first (see Recommendation 7). Providers should taper benzodiazepines gradually if discontinued because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death (contextual evidence review). A commonly used tapering schedule that has been used safely and with moderate success is a reduction of the benzodiazepine dose by 25% every 1–2 weeks (199,200). CBT increases tapering success rates and might be particularly helpful for patients struggling with a benzodiazepine taper (199). If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., CBT) and/or specific antidepressants or other nonbenzodiazepine medications approved for anxiety should be offered. Experts emphasized that providers should communicate with mental health professionals managing the patient to coordinate care.

12. Providers should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder (recommendation category: A, evidence type: 3).

Opioid use disorder (previously classified as opioid abuse or opioid dependence) is defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) as a problematic pattern of opioid use leading to clinically significant impairment or distress, manifested by at least two defined criteria occurring within a year (see <http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf>) (16).

The clinical evidence review found prevalence of opioid dependence in primary care settings among patients with chronic pain on opioid therapy to be 3%–26% (KQ2). As found in the contextual evidence review and supported by moderate quality evidence, opioid agonist or partial agonist treatment with methadone maintenance therapy or buprenorphine in combination with psychosocial treatment has been shown to be more effective in preventing relapse among patients with opioid use disorder than detoxification without maintenance medication (141–144). However, the cited studies primarily evaluated patients with a history of illicit opioid use, rather than prescription opioid use for chronic pain, and studies of referral to treatment from primary care after opioid therapy for chronic pain are limited (201,202); thus, the evidence of effectiveness for referral to treatment for opioid dependence in patients with chronic pain is indirect and graded as low (type 3). Treatment need in a community is often not met by capacity to provide buprenorphine or methadone maintenance therapy (203), and patient cost can be a barrier to buprenorphine treatment because insurance coverage of buprenorphine for opioid use disorder is often limited (204). Oral or long-acting injectable formulations of naltrexone can also be used as medication-assisted treatment for opioid use disorder in nonpregnant adults, particularly for highly

motivated persons (205,206). Experts agreed that providers prescribing opioids should identify treatment resources for opioid use disorder in the community and should work together to ensure sufficient treatment capacity for opioid use disorder at the practice level.

If providers suspect opioid use disorder based on patient concerns or behaviors or on findings in prescription drug monitoring program data (Recommendation 9) or from urine drug testing (Recommendation 10), they should discuss their concern with their patient and provide an opportunity for the patient to disclose related concerns or problems. Providers should assess for the presence of opioid use disorder using DSM-5 criteria (16). Alternatively, providers can arrange for a substance use disorder treatment specialist to assess for the presence of opioid use disorder. For patients meeting criteria for opioid use disorder, providers should offer or arrange for patients to receive evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone maintenance therapy in combination with behavioral therapies). Providers should also consider offering naloxone to patients with opioid use disorder (see Recommendation 8). For patients with problematic opioid use that does not meet criteria for opioid use disorder, experts noted that providers can offer to taper and discontinue opioids (see Recommendation 7). For patients who choose to but are unable to taper, providers may reassess for opioid use disorder and offer opioid agonist therapy if criteria are met.

Physicians not already certified to provide buprenorphine in an office-based setting can undergo training to receive a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) that allows them to prescribe buprenorphine to treat patients with opioid use disorder. Physicians prescribing opioids in communities without sufficient treatment capacity for opioid use disorder should strongly consider obtaining this waiver. Information about qualifications and the process to obtain a waiver are available from SAMHSA (207). Additional guidance has been published previously (208) on induction, use, and monitoring of buprenorphine treatment for opioid use disorder (see part 5) and on goals, components of, and types of effective psychosocial treatment that are recommended in conjunction with pharmacological treatment of opioid use disorder (see Part 7).

Providers unable to provide treatment themselves should arrange for patients with opioid use disorder to receive care from a substance use disorder treatment specialist, such as an office-based buprenorphine treatment provider or an opioid treatment program specialist, who can provide medication-assisted therapy. Providers should assist patients in finding qualified treatment providers and should arrange for patients to follow up with these providers, as well as arranging for ongoing coordination of care. Providers should not dismiss patients from their practice because of a substance use disorder because this can adversely affect patient safety and could represent patient abandonment. Identification of substance use disorder represents an opportunity for a provider to initiate potentially life-saving interventions, and it is important for the provider to collaborate with the patient regarding their safety to increase the likelihood of successful treatment. In addition, although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Providers should continue to use nonpharmacologic and nonopioid pharmacologic pain treatments as appropriate (see Recommendation 1) and consider consulting a pain specialist as needed to provide optimal pain management.

Resources to help with arranging for treatment include SAMHSA's buprenorphine physician locator (http://buprenorphine.samhsa.gov/bwns_locator/); SAMHSA's Opioid Treatment Program Directory (<http://dpt2.samhsa.gov/treatment/directory.aspx>); SAMHSA's Provider Clinical Support System for Opioid Therapies (<http://pcss-o.org>), which offers extensive experience in the treatment of substance use disorders and specifically of opioid use disorder, as well as expertise on the interface of pain and opioid misuse; and SAMHSA's Provider's Clinical Support System for Medication-Assisted Treatment

(<http://pcssmat.org>), which offers expert physician mentors to answer questions about assessment for and treatment of substance use disorders.

Conclusions and Future Directions

Clinical guidelines represent one strategy for improving prescribing practices and health outcomes. Efforts are required to disseminate the guideline and achieve widespread adoption and implementation of the recommendations in clinical settings. CDC will translate this guideline into user-friendly materials for distribution and use by health systems, medical professional societies, insurers, public health departments, health information technology developers, and providers and engage in dissemination efforts. Activities such as development of clinical decision support in electronic health records to assist providers' treatment decisions at the point of care, identification of mechanisms that insurers and pharmacy benefit plan managers can use to promote safer prescribing within plans, provider education, and development of clinical quality improvement measures and initiatives to improve prescribing and patient care within health systems have promise for increasing guideline adoption and improving practice. In addition, policy initiatives that address barriers to implementation of the guidelines, such as accessibility of PDMP data, availability of providers of medication-assisted treatment for opioid use disorder, insurance coverage for nonpharmacologic treatments and appropriate urine drug testing, and reimbursable time for patient counseling might likewise be effective in enhancing implementation of the recommended practices. As highlighted in the forthcoming report on the National Pain Strategy, an overarching federal effort that outlines a comprehensive population-level health strategy for addressing pain as a public health problem, clinical guidelines complement other strategies aimed at preventing illnesses and injuries that lead to pain. These strategies include strengthening the evidence base for pain prevention and treatment strategies, reducing disparities in pain treatment, improving service delivery and reimbursement, supporting professional education and training, and providing public education. It is important that overall improvements be made in developing the workforce to address pain management in general, in addition to opioid prescribing specifically.

This guideline provides recommendations that are based on the best available evidence that was interpreted and informed by expert opinion. The clinical scientific evidence informing the recommendations is low in quality. To inform future guideline development, more research is necessary to fill in critical evidence gaps. The evidence reviews forming the basis of this guideline clearly illustrate that there is much yet to be learned about the effectiveness, safety, and economic efficiency of long-term opioid therapy. As highlighted by an expert panel in a recent workshop sponsored by the National Institutes of Health on the role of opioid pain medications in the treatment of chronic pain, "evidence is insufficient for every clinical decision that a provider needs to make about the use of opioids for chronic pain" (209). The National Institutes of Health panel recommended that research is needed to improve our understanding of which types of pain, specific diseases, and patients are most likely to be associated with benefit and harm from opioid pain medications; evaluate multidisciplinary pain interventions; estimate cost-benefit; develop and validate tools for identification of patient risk and outcomes; assess the effectiveness and harms of opioid pain medications with alternative study designs; and investigate risk identification and mitigation strategies and their effects on patient and public health outcomes. Research that contributes to safer and more effective pain treatment can be implemented across public health entities and federal agencies (4). Additional research can inform the development of future guidelines for special populations that could not be adequately addressed in this guideline, such as children and adolescents, where evidence and guidance is needed but currently lacking. Yet, given that chronic pain is recognized as a significant public health problem, the risks associated with long-term opioid therapy, the availability of effective alternative treatment options for pain, and the potential for improvement in the quality of health care with the implementation of recommended practices, a guideline for prescribing is warranted with the evidence that is currently available. The tradeoff between

the benefits and the risks of long-term opioid therapy for chronic pain based on both clinical and contextual evidence is sufficiently clear to support the issuance of category A recommendations in most cases. CDC will revisit this guideline as needed to determine if evidence gaps have been sufficiently closed to warrant an update of the guideline. Until this research is conducted, clinical practice guidelines will have to be based on the best available evidence and expert opinion. This guideline is intended to improve communication between providers and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including abuse, dependence, overdose, and death.

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National Center for Injury Prevention and Control, and Leonard J. Paulozzi, MD, Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control.

*A list of the members appears on page 51.

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BOX 1. CDC recommendations for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care

Determining When to Initiate or Continue Opioids for Chronic Pain

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Providers should only consider adding opioid therapy if expected benefits for both pain and function are anticipated to outweigh risks to the patient.
2. Before starting opioid therapy for chronic pain, providers should establish treatment goals with all patients, including realistic goals for pain and function. Providers should not initiate opioid therapy without consideration of how therapy will be discontinued if unsuccessful. Providers should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, providers should discuss with patients known risks and realistic benefits of opioid therapy and patient and provider responsibilities for managing therapy.

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

4. When starting opioid therapy for chronic pain, providers should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, providers should prescribe the lowest effective dosage. Providers should use caution when prescribing opioids at any dosage, should implement additional precautions when increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day, and should generally avoid increasing dosage to ≥ 90 MME/day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, providers should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three or fewer days usually will be sufficient for most nontraumatic pain not related to major surgery.
7. Providers should evaluate benefits and harms with patients within 1–4 weeks of starting opioid therapy for chronic pain or of dose escalation. Providers should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, providers should work with patients to reduce opioid dosage and to discontinue opioids.

Assessing Risk and Addressing Harms of Opioid Use

8. Before starting and periodically during continuation of opioid therapy, providers should evaluate risk factors for opioid-related harms. Providers should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, or higher opioid dosage (≥ 50 MME) are present.
9. Providers should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving high opioid dosages or dangerous combinations that put him or her at high risk for overdose. Providers should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10. When prescribing opioids for chronic pain, providers should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.

11. Providers should avoid prescribing opioid pain medication for patients receiving benzodiazepines whenever possible.
12. Providers should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

* All recommendations are category A (apply to all patients outside of active cancer treatment, palliative care, and end-of-life care) except recommendation 10 (designated category B, with individual decision making required); see full guideline for evidence ratings.

BOX 2. Interpretation of recommendation categories and evidence type

Recommendation Categories

Based on evidence type, balance between desirable and undesirable effects, values and preferences, and resource allocation (cost).

Category A recommendation: Applies to all persons; most patients should receive the recommended course of action.

Category B recommendation: Individual decision making needed; different choices will be appropriate for different patients. Providers help patients arrive at a decision consistent with patient values and preferences and specific clinical situations.

Evidence Type

Based on study design as well as a function of limitations in study design or implementation, imprecision of estimates, variability in findings, indirectness of evidence, publication bias, magnitude of treatment effects, dose-response gradient, and constellation of plausible biases that could change effects.

Type 1 evidence: Randomized controlled trials or overwhelming evidence from observational studies.

Type 2 evidence: Randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies.

Type 3 evidence: Observational studies or randomized controlled trials with notable limitations.

Type 4 evidence: Clinical experience and observations, observational studies with important limitations, or randomized controlled trials with several major limitations.

Steering Committee and Core Expert Group Members

Steering Committee: Deborah Dowell, MD, Tamara M. Haegerich, PhD; Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC; Roger Chou, MD; Oregon Health and Sciences University

Core Expert Group Members: Pam Archer, MPH, Oklahoma State Department of Health; Jane Ballantyne, MD; University of Washington (retired); Amy Bohnert, PhD; University of Michigan; Bonnie Burman, ScD; Ohio Department on Aging; Roger Chou, MD; Oregon Health and Sciences University; Phillip Coffin, MD, San Francisco Department of Public Health; Gary Franklin, MD, MPH; Washington State Department of Labor and Industries/University of Washington; Erin Krebs, MDH; Minneapolis VA Health Care System/University of Minnesota; Mitchel Mutter, MD, Tennessee Department of Health; Lewis Nelson, MD; New York University School of Medicine; Trupti Patel, MD, Arizona Department of Health Services; Christina A. Porucznik, PhD, University of Utah; Robert “Chuck” Rich, MD, FAFAP, American Academy of Family Physicians; Joanna Starrels, MD, Albert Einstein College of Medicine of Yeshiva University; Michael Steinman, MD, Society of General Internal Medicine; Thomas Tape, MD, American College of Physicians; Judith Turner, PhD, University of Washington

Roger Chou, MD assisted in the review of the scientific evidence and authorship of the guideline under a short-term detail through an Intergovernmental Personnel Act (IPA) appointment.

Core Expert Group (CEG) Disclosures

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Stakeholder Review Group

John Markman, MD, American Academy of Neurology; Bob Twillman, PhD, American Academy of Pain Management; Edward C. Covington, MD, American Academy of Pain Medicine; Roger F. Suchyta, MD, FAAP, American Academy of Pediatrics; Kavitha V. Neerukonda, JD, American Academy of Physical Medicine and Rehabilitation; Mark Fleury, PhD, American Cancer Society Cancer Action Network; Penney Cowan, American Chronic Pain Association; David Juurlink, BPharm, MD, PhD, American College of Medical Toxicology; Gerald “Jerry” F. Joseph, Jr, MD, American College of Obstetrics and Gynecology; Bruce Ferrell, MD, AGSF, M. Carrington Reid, MD, PhD, American Geriatrics Society; Ashley Thompson, American Hospital Association; Barry D. Dickinson, PhD, American Medical Association; Gregory Terman MD, PhD, American Pain Society; Beth Haynes, MPPA, American Society of Addiction Medicine; Asokumar Buvanendran, MD, American Society of Anesthesiologists; Robert M. Plovnick; MD, American Society of Hematology; Sanford M. Silverman, MD, American Society of Interventional Pain Physicians; Andrew Kolodny, MD, Physicians for Responsible Opioid Prescribing.

The recommendations and all statements included in this guideline are those of CDC and do not necessarily represent the official position of any persons or organizations comprising the Stakeholder Review Group.

Peer Reviewers

Jeanmarie Perrone, MD, University of Pennsylvania; Matthew Bair, MD, Indiana University School of Medicine; David Tauben, MD, University of Washington

TABLE. Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical evidence review ratings of the evidence for the key clinical questions regarding effectiveness and risks of long-term opioid therapy for chronic pain

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of evidence	Other factors	Estimates of effect/findings
Effectiveness and comparative effectiveness (KQ1)							
Effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (>1 year) outcomes							
Pain, function, and quality of life	None	—†	—	—	Insufficient	—	No evidence
Harms and adverse events (KQ2)							
Risks of opioids versus placebo or no opioids on opioid abuse, addiction, and related outcomes; overdose; and other harms							
Abuse or addiction	1 cohort study (n = 568,640)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	One retrospective cohort study found long-term use of prescribed opioids associated with an increased risk of abuse or dependence diagnosis versus no opioid use (adjusted OR ranged from 14.9 to 122.5, depending on dose).
Abuse or addiction	10 uncontrolled studies (n = 3,780)	Very serious limitations	Very serious inconsistency	No imprecision	4	None identified	In primary care settings, prevalence of opioid abuse ranged from 0.6% to 8% and prevalence of dependence from 3% to 26%. In pain clinic settings, prevalence of misuse ranged from 8% to 16% and addiction from 2% to 14%. Prevalence of aberrant drug-related behaviors ranged from 6% to 37%.
Overdose	1 cohort study (n = 9,940)	Serious limitations	Unknown (1 study)	Serious imprecision	3	None identified	Current opioid use associated with increased risk of any overdose events (adjusted HR 5.2, 95% CI = 2.1–12) and serious overdose events (adjusted HR 8.4, 95% CI = 2.5–28) versus current nonuse.
Fractures	1 cohort study (n = 2,341) and 1 case-control study (n = 21,739 case patients)	Serious limitations	No inconsistency	No imprecision	3	None identified	Opioid use associated with increased risk of fracture in 1 cohort study (adjusted HR 1.28, 95% CI = 0.99–1.64) and 1 case-control study (adjusted OR 1.27, 95% CI = 1.21–1.33).
Myocardial infarction	1 cohort study (n = 426,124) and 1 case-control study (n = 11,693 case patients)	No limitations	No inconsistency	No imprecision	3	None identified	Current opioid use associated with increased risk of myocardial infarction versus nonuse (adjusted OR 1.28, 95% CI = 1.19–1.37 and incidence rate ratio 2.66, 95% CI = 2.30–3.08).
Endocrinologic harms	1 cross-sectional study (n = 11,327)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	Long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement versus nonuse (adjusted OR 1.5, 95% CI = 1.1–1.9).
How do harms vary depending on the opioid dose used?							

Abuse or addiction	1 cohort study (n = 568,640)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	One retrospective cohort study found higher doses of long-term opioid therapy associated with increased risk of opioid abuse or dependence than lower doses. Compared to no opioid prescription, the adjusted odds ratios were 15 (95% CI = 10–21) for 1 to 36 MME/day, 29 (95% CI = 20–41) for 36 to 120 MME/day, and 122 (95% CI = 73–205) for \geq 120 MME/day.
Overdose	1 cohort study (n = 9,940) and 1 case-control study (n = 593 case patients in primary analysis)	Serious limitations	No inconsistency	No imprecision	3	Magnitude of effect, dose response relationship	Versus 1 to 19 MME/day, one cohort study found an adjusted HR for an overdose event of 1.44 (95% CI = 0.57–3.62) for 20 to 49 MME/day that increased to 11.18 (95% CI = 4.80–26.03) at $>$ 100 MME/day; one case-control study found an adjusted OR for an opioid-related death of 1.32 (95% CI = 0.94–1.84) for 20 to 49 MME/day that increased to 2.88 (95% CI = 1.79–4.63) at \geq 200 MME/day.
Fractures	1 cohort study (n = 2,341)	Serious limitations	Unknown (1 study)	Serious imprecision	3	None identified	Risk of fracture increased from an adjusted HR of 1.20 (95% CI = 0.92–1.56) at 1 to $<$ 20 MME/day to 2.00 (95% CI = 1.24–3.24) at \geq 50 MME/day; the trend was of borderline statistical significance.
Myocardial infarction	1 cohort study (n = 426,124)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	Relative to a cumulative dose of 0 to 1,350 MME during a 90-day period, the incidence rate ratio for myocardial infarction for 1350 to $<$ 2700 MME was 1.21 (95% CI = 1.02–1.45), for 2,700 to $<$ 8,100 MME was 1.42 (95% CI = 1.21–1.67), for 8,100 to $<$ 18,000 MME was 1.89 (95% CI = 1.54–2.33), and for $>$ 18,000 MME was 1.73 (95% CI = 1.32–2.26).
Motor vehicle crash injuries	1 case-control study (n = 5,300 case patients)	No limitations	Unknown (1 study)	No imprecision	3	None identified	No association between opioid dose and risk of motor vehicle crash injuries.
Endocrinologic harms	1 cross-sectional study (n = 11,327) New for update: 1 additional cross-sectional study (n=1,585)	Serious limitations	Consistent	No imprecision	3	None identified	Relative to 0 to $<$ 20 MME/day, the adjusted OR for \geq 120 MME/day for use of medications for erectile dysfunction or testosterone replacement was 1.6 (95% CI = 1.0–2.4). One new cross-sectional study found higher-dose long-term opioid therapy associated with increased risk of androgen deficiency among men receiving immediate-release opioids (adjusted OR per 10 MME/day 1.16, 95% CI = 1.09–1.23), but the dose response was very weak among men receiving ER/LA opioids.

Dosing strategies (KQ3)							
Comparative effectiveness of different methods for initiating opioid therapy and titrating doses							
Pain	3 randomized trials (n = 93)	Serious limitations	Serious inconsistency	Very serious imprecision	4	None identified	Trials on effects of titration with immediate-release versus ER/LA opioids reported inconsistent results and had additional differences between treatment arms in dosing protocols (titrated versus fixed dosing) and doses of opioids used.
Overdose	New for update: 1 cohort study (n = 840,606)	Serious limitations	Unknown (1 study)	No imprecision	4	None identified	One new cross-sectional study found initiation of therapy with an ER/LA opioid associated with increased risk of overdose versus initiation with an immediate-release opioid (adjusted HR 2.33, 95% CI = 1.26–4.32).
Comparative effectiveness of different ER/LA opioids							
Pain and function	3 randomized trials (n = 1,850)	Serious limitations	No inconsistency	No imprecision	3	None identified	No differences
All-cause mortality	1 cohort study (n = 108,492) New for update: 1 cohort study (n = 38,756)	Serious limitations	Serious inconsistency	No imprecision	4	None identified	One cohort study found methadone to be associated with lower all-cause mortality risk than sustained-release morphine in a propensity-adjusted analysis (adjusted HR 0.56, 95% CI = 0.51–0.62) and one cohort study among Tennessee Medicaid patients found methadone to be associated with higher risk of all-cause mortality than sustained-release morphine (adjusted HR 1.46, 95% CI = 1.17–1.73).
Abuse and related outcomes	1 cohort study (n = 5,684)	Serious limitations	Unknown (1 study)	Serious imprecision	4	None identified	One cohort study found some differences between ER/LA opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions.
Long- versus immediate-release opioids							
Endocrinologic harms	New for update: 1 cross-sectional study (n = 1,585)	Serious limitations	Unknown (1 study)	No imprecision	4	None identified	One cross-sectional study found ER/LA opioids associated with increased risk of androgen deficiency versus immediate-release opioids (adjusted OR 3.39, 95% CI = 2.39–4.77).
Dose escalation versus dose maintenance or use of dose thresholds							
Pain, function, or withdrawal due to opioid misuse	1 randomized trial (n = 140)	Serious limitations	Unknown (1 study)	Very serious imprecision	3	None identified	No difference between more liberal dose escalation versus maintenance of current doses in pain, function, or risk of withdrawal due to opioid misuse, but there was limited separation in opioid doses between groups (52 versus 40 MME/day at the end of the trial).

Immediate-release versus ER/LA opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled and continuous versus as-needed dosing of opioids; or opioid rotation versus maintenance of current therapy							
Pain, function, quality of life, and outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effects of decreasing or tapering opioid doses versus continuation of opioid therapy							
Pain and function	1 randomized trial (n = 10)	Very serious limitations	Unknown (1 study)	Very serious imprecision	4	None identified	Abrupt cessation of morphine was associated with increased pain and decreased function compared with continuation of morphine.
Comparative effectiveness of different tapering protocols and strategies							
Opioid abstinence	2 nonrandomized trials (n = 150)	Very serious limitations	No inconsistency	Very serious imprecision	4	None identified	No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3–6 months
Risk assessment and risk mitigation strategies (KQ4)							
Diagnostic accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse among patients with chronic pain being considered for long-term opioid therapy							
Opioid risk tool	3 studies of diagnostic accuracy (n = 496) New for update: 2 studies of diagnostic accuracy (n = 320)	Serious limitations	Very serious inconsistency	Serious imprecision	4	None identified	Based on a cutoff score of >4 (or unspecified), five studies (two fair-quality, three poor-quality) reported sensitivity that ranged from 0.20 to 0.99 and specificity that ranged from 0.16 to 0.88).
Screener and Opioid Assessment for Patients with Pain, Version 1	2 studies of diagnostic accuracy (n = 203)	Very serious limitations	No inconsistency	Serious imprecision	3	None identified	Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity was 0.38 in one study, for a positive likelihood ratio of 1.11 and a negative likelihood ratio of 0.83. Based on a cutoff score of >6, sensitivity was 0.73 in one study.
Screener and Opioid Assessment for Patients with Pain- Revised	New for update: 2 studies of diagnostic accuracy (n = 320)	Very serious limitations	No inconsistency	Serious imprecision	3	None identified	Based on a cutoff score of >3 or unspecified, sensitivity was 0.25 and 0.53 and specificity was 0.62 and 0.73 in two studies, for likelihood ratios close to 1.
Brief Risk Interview	New for update: 2 studies of diagnostic accuracy (n = 320)	Very serious limitations	No inconsistency	Serious imprecision	3	None identified	Based on a “high risk” assessment, sensitivity was 0.73 and 0.83 and specificity was 0.43 and 0.88 in two studies, for positive likelihood ratios of 1.28 and 7.18 and negative likelihood ratios of 0.63 and 0.19.
Effectiveness of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse in patients with chronic pain							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effectiveness of risk mitigation strategies, including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations, on outcomes related to overdose, addiction, abuse, or misuse							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effectiveness of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse in patients with chronic pain							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence

Effectiveness of risk mitigation strategies, including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations, on outcomes related to overdose, addiction, abuse, or misuse							
Outcomes related to abuse	None	–	–	–	Insufficient	–	No evidence
Comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids							
Outcomes related to abuse	None	–	–	–	Insufficient	–	No evidence
Effects of opioid therapy for acute pain on long-term use (KQ5)							
Long-term opioid use	New for update: 2 cohort studies (n = 399,852)	Serious limitations	No inconsistency	No imprecision	3	None identified	One study found use of opioids within 7 days of low-risk surgery associated with increased likelihood of opioid use at 1 year (adjusted OR 1.44, 95% CI = 1.39–1.50), and one study found use of opioids within 15 days of onset of low back pain among workers with a compensation claim associated with increased risk of late opioid use (adjusted OR 2.08, 95% CI = 1.55–2.78 for 1 to 140 MME/day and OR 6.14, 95% CI = 4.92–7.66 for ≥450 MME/day).

Abbreviations: CI = confidence interval; HR = hazard ratio; MME = morphine milligram equivalents; OR = odds ratio.

*Ratings were made per GRADE quality assessment criteria; “no limitations” indicates that limitations assessed through the GRADE method were not identified.

†Not applicable as no evidence was available for rating

Appendix 1 online only

Appendix 2 online only



California State Board of Pharmacy

1625 N. Market Blvd, Suite N219, Sacramento, CA 95834
Phone (916) 574-7900
Fax (916) 574-8618
www.pharmacy.ca.gov

BUSINESS, CONSUMER SERVICES AND HOUSING AGENCY
DEPARTMENT OF CONSUMER AFFAIRS
GOVERNOR EDMUND G. BROWN JR.

January 13, 2016

Submitted via: <https://www.federalregister.gov/articles/2015/12/14/2015-31375/proposed-2016-guideline-for-prescribing-opioids-for-chronic-pain#open-comment>

Re: Centers for Disease Control and Prevention, Docket No. CDC-2015-0112

The California State Board of Pharmacy writes this letter in support of the Center for Disease Control and Prevention's draft guidelines for Prescribing Opioids for Chronic Pain. We recognize and acknowledge the substantial effort which the CDC committed to producing these guidelines. We believe they provide meaningful direction and guidance to prescribers and dispensers, and will greatly benefit public health.

The California State Board of Pharmacy is the nation's largest board of pharmacy. We regulate over 140,000 businesses and individuals that dispense, compound, store, ship and transport prescription drugs and prescription devices to patients, practitioners and health care facilities within and outside California. This includes pharmacies, sterile compounding pharmacies, pharmacists, drug wholesalers. The board is mandated to address public safety needs first, a mandate the board takes seriously.

The board has been a strong advocate of addressing prescription drug abuse, an area we recognize that the CDC has declared an epidemic in the US. We have been aggressive in identifying and removing practitioners who failed to exercise their required corresponding responsibility to ensure medication dispensed, even when prescribed, is appropriate for the patient. We have conducted educational sessions and conferences, and developed materials to educate licensees about this topic. The board has also worked with a number of agencies to produce and share consumer and licensee materials on the topic.

As the nation transitions away from the widespread prescribing and dispensing of opioids, prescribers and dispensers look for guidance. In California, the California Medical Board revised *Guidelines for Prescribing Controlled Substances for Pain* in late 2014. Your guidance document will provide additional, much needed, guidance to pharmacists as they exercise their corresponding responsibility to ensure that medication dispensed by pharmacies, and patient care provided by pharmacists is appropriate. It will also enable pharmacists to work with prescribers in developing and supporting strong patient care.

Once finalized, the board will aid in the dissemination of this information to our licensees and to the public. The succinct presentation provided in Box 1 Recommendations for Prescribing Opioids for Chronic Pain Outside of Active Cancer, Palliative and End-of-Life Care is well-designed for such education.

We congratulate the CDC on the development of this guideline. Thank you.

Sincerely,

A handwritten signature in black ink that reads "Virginia Herold". The signature is fluid and cursive, with the first name being the most prominent.

Virginia Herold

Executive Officer

California State Board of Pharmacy

Attachment 1



Clinical Review: Morphine Equivalent Daily Dose to Prevent Opioid Overuse

Learning Objectives:

- Define morphine equivalent daily dose (MEDD) and how it is being used to indicate potential dose-related risk for prescription opioid overdose.
- Describe high-risk prescribing of prescription opioids within the Medi-Cal fee-for-service program.
- Summarize best practices for responsible opioid prescribing.

Key Points:

- While there is no completely safe dose of opioids, MEDD can be used as an indicator of potential dose-related risk for adverse drug reactions, including overdose.
- While there are differing opinions as to the maximum MEDD threshold that should trigger additional action by clinicians, the Medical Board of California (MBC) recommends proceeding cautiously once the MEDD reaches 80 mg.
- In the Medi-Cal fee-for-service population, the vast majority (87%) of paid claims for opioids were well under the 80 mg MEDD threshold recommended by the MBC for a yellow flag warning.
- Online MEDD calculators are available to help clinicians determine morphine milligram equivalency. These calculators are not intended for dosage conversion from one product to another, but can be used to assess the comparative potency of opioids using a morphine equivalency standard.
- All providers who prescribe opioids need to enroll in and access California's prescription drug monitoring program, available on the [Controlled Substance Utilization Review and Evaluation System \(CURES\)](#) Web page of the Office of the Attorney General website. In order to be most effective, MEDD calculations need to include all opioid prescriptions written for a patient, including those written by other providers.

Background

Each day in the United States, 46 people die from an overdose of prescription opioid or narcotic pain relievers.¹ The Centers for Disease Control and Prevention (CDC) describes the following groups as particularly vulnerable to prescription opioid overdose: 1) people who obtain multiple controlled substance prescriptions from multiple providers; 2) those who take high daily dosages of prescription painkillers and those who misuse multiple abuse-prone prescription drugs, especially other CNS depressants, such as benzodiazepines, carisoprodol, or other sedatives; 3) low-income people and those living in rural areas; and 4) people with mental illness and/or those with a history of substance abuse.²

Morphine Equivalent Daily Dose (MEDD)

Recent studies demonstrate that a patient's cumulative MEDD is an indicator of potential dose-related risk for adverse drug reactions to opioids, including overdose.^{3,4} The terminology for daily morphine equivalency may vary depending on the resource used, and may be described as MEDD, morphine equivalent dose (MED), or morphine milligram equivalents (MME). **Daily morphine milligram equivalents are used to assess comparative potency, but not to convert a particular opioid dosage from one product to another.** The calculation to determine morphine milligram equivalents includes drug strength, quantity, days' supply and a defined conversion factor unique to each drug. By converting the dose of an opioid to a morphine

equivalent dose, a clinician can determine whether a cumulative daily dose of opioids approaches an amount associated with increased risk.

Online calculators are available to estimate MEDD. **It should be noted again that these calculators are not intended for dosage conversion from one product to another, but only to assess the comparative potency of opioids.** Furthermore, calculated morphine equivalency may vary between tools for certain drugs, depending on the algorithm used. Commonly used websites that offer MEDD calculators include the following:

- [Washington State Agency Medical Directors' Group](#)
- [Prescription Drug Monitoring Program Training and Technical Assistance Center \(PDMP TTAC\)](#)
- [The New York City Department of Health and Mental Hygiene](#)

Equianalgesic dose ratios are only approximations and do not account for genetic factors, incomplete cross-tolerance between various opioids, and variable pharmacokinetics that may affect relative potency. If used to estimate a conversion, it is recommended that after calculating the appropriate conversion dose, the prescribed dose be reduced by 25 – 50% to assure patient safety.⁴

Compared with patients receiving an MEDD of 1 – 20 mg, who had a 0.2% annual overdose rate, patients receiving an MEDD of 100 mg or more had almost nine times as much risk of overdose and a 1.8% annual overdose rate as compared to the lowest doses.³ The CDC review of opioid prescribing and overdose found that among patients who are prescribed opioids, an estimated 80% are prescribed low doses (<100 mg MEDD) by a single provider, and these patients account for an estimated 20% of all prescription drug overdoses. Another 10% of patients are prescribed high doses (≥100 mg MEDD) of opioids by single prescribers and account for an estimated 40% of prescription opioid overdoses. The remaining 10% of patients seek care from multiple doctors, are prescribed high daily doses, and account for another 40% of opioid overdoses.⁵

While there are differing opinions among experts and organizations as to the maximum MEDD threshold that should trigger additional action by clinicians (Table 1), the MBC recommends proceeding cautiously (a yellow flag warning) once the MEDD reaches 80 mg.⁶ There is no completely safe opioid dose.

Table 1. Selected Organizations' MEDD Thresholds and Recommended Actions

Year	Organization	MEDD Threshold (mg/day)	Recommended Action at MEDD Threshold
2010	American Academy of Pain Medicine ⁷	>200	Increase frequency and intensity of monitoring
2010	Utah State Clinical Guidelines ⁸	>120 – 200	Increase clinical vigilance
2010	Veterans Affairs/Department of Defense ⁹	>200	Refer or consult
2010, 2015	Washington State Agency Medical Directors' Group ⁴	>120	Consult from pain management expert
2011	Canadian Guidelines ¹⁰	>200	Reassess or monitor
2011, 2014	American College of Occupational and Environmental Medicine ¹¹	≥50	Follow up frequently; document improved function
2011	New York City Department of Health and Mental Hygiene ¹²	>100	Reassess pain status or consider other approaches
2012	American Society of Interventional Pain Physicians ¹³	>91	Consider pain management consultation
2012	Centers for Medicare and Medicaid Services ¹⁴	>120	Consider case management
2014	Medical Board of California ⁶	≥80	Proceed cautiously and consider referral to specialist when higher doses are contemplated
2015	California Division of Workers' Compensation ¹⁵	≥80	Increase clinical monitoring, consider specialty referral, attempt to wean to lower dose.

In addition, as of federal fiscal year 2013 (FFY 2013), nine state Medicaid programs reported having an established policy with a recommended maximum MEDD (Table 2).¹⁶

Table 2. State Medicaid Drug Use Review (DUR) Programs with Established Recommendations for Maximum MEDD

State	MEDD Threshold (mg/day)	Additional Information
Delaware	120	All long-acting opioids require prior authorization. The total dose for all narcotic therapy must be <120 mg MEDD.
Kansas	200	
Massachusetts	360	Individual dose limits for each opioid were determined based on utilization trends.
Maine	30	Prior authorization is required for any dose over 30mg; maximum allowable dose 300 mg
Michigan	30	
North Carolina	750	Maximum allowable dose
Oregon	120	
Washington	120	Based on Agency Medical Directors Association Interagency Guidelines
Wyoming	120	

Both Massachusetts and Washington have described in detail the impact of implementing an established policy and predetermined maximum MEDD threshold for triggering a detailed patient review.^{17,18} Massachusetts defined a specific maximum MEDD for oxycodone, fentanyl, morphine,

and methadone (they selected two standard deviations outside the mean dose noted in their drug utilization review). In addition to requiring prior authorization for the specified dose, a multidisciplinary team including a physician, pharmacist, and behavioral specialist reviewed high-dose utilization profiles every two weeks. The team participated in phone interventions for clarification of prior authorization requests, treatment care plans, or specific restrictions. Over a three-year period (2002 – 2005), the number of unique utilizers decreased by 17.8% (p <0.0001) and the number of claims by 4.1% (p <0.0001).¹⁷ Claims for oxycodone decreased by 34.9% and claims for fentanyl decreased by 25%.¹⁷

In 2007, the Washington State Agency Medical Directors' Group, which represents all public payers in Washington, developed a collaborative interagency guideline on opioid dosing (updated in June 2015).⁴ The guideline recommends that at an MEDD of 120 mg providers must obtain consultation from a pain medicine expert for patients whose pain and function have not substantially improved as a result of opioid treatment. An evaluation of the impact of the guideline was conducted through 2010, and showed the number of prescriptions for Schedule II opioids plateaued during 2006 – 2008, then declined sharply in 2009 and 2010.⁷ The total number of paid prescriptions for Schedule III opioids had peaked in 1999 (93,550), then declined through 2008 (79,882), 2009 (63,808) and 2010 (52,499).⁷ The average MEDD among beneficiaries declined from a peak of 144.7 in 2002 to 105 in 2010.¹⁸

MEDD in the Medi-Cal Fee-For-Service Population

A retrospective cohort study was conducted to calculate the MEDD for all paid pharmacy claims for prescription opioid medications in the Medi-Cal fee-for-service population (dates of service between July 1, 2014, and June 30, 2015). The National Drug Code (NDC), days supply, and drug quantity fields were extracted from Medi-Cal pharmacy claims data and matched (via NDC) to the drug strength and MME conversion factor using the Morphine Equivalent Calculator Tool developed by the PDMP TTAC at Brandeis University, in collaboration with the CDC.

The following equation was used to calculate MEDD:

$$\frac{(\text{Drug Strength}) \times (\text{Drug Quantity}) \times (\text{MME Conversion Factor})}{(\text{Days Supply})}$$

All instructions for MEDD calculation were followed using the technical assistance guide provided by the PDMP TTAC.¹⁹

An additional analysis was performed on a subset of Medi-Cal fee-for-service beneficiaries who were continuously eligible in the Medi-Cal fee-for-service program between January 1, 2015, and June 30, 2015, and who had at least one paid claim for a prescription opioid medication between April 1, 2015, and June 30, 2015 (the measurement period). Medical and pharmacy claims data were reviewed for all beneficiaries in the study population with a calculated cumulative morphine equivalent dose >120 mg for at least one day during the measurement period. Data fields specifying diagnostic codes and place of service were extracted from medical claims data and were used to identify those beneficiaries in the study population who had a primary or secondary diagnosis of cancer and/or who were receiving hospice care.

Descriptive statistics were used to summarize MEDD values and claims data. Data analyses were performed using IBM® SPSS®, version 23.0 (Chicago, IL).

Results

Between July 1, 2014, and June 30, 2015, a total of 529,681 paid pharmacy claims for prescription opioid medications were filled by a total of 262,017 Medi-Cal fee-for-service beneficiaries. The summary of paid claims exceeding MEDD thresholds of 80 mg, 100 mg, and 120 mg for all paid claims is shown in Table 3. Also shown in Table 3 is the distribution among a subset of paid claims with a days supply >14 days, as over half (56%) of all paid claims for opioids between July 1, 2014, and June 30, 2015, were for a days supply ≤7 days.

Table 3. Total Paid Claims Exceeding Recommended MEDD Thresholds in the Medi-Cal Fee-For-Service Population (Dates of Service Between July 1, 2014, and June 30, 2015)

	Recommended MEDD Thresholds		
	>80 mg/day	>100 mg/day	>120 mg/day
Total paid claims (n = 529,681)	71,236 (13.4%)	58,741 (11.1%)	47,769 (9.0%)
Total paid claims >14 days supply (n = 237,106)	62,596 (26.4%)	54,060 (22.8%)	43,865 (18.5%)

The vast majority of paid claims for opioids were well under the 80 mg/day threshold recommended by the MBC for a yellow flag warning (87% of all paid claims and 74% of paid claims >14 days supply). However, during one year there were 47,769 paid claims identified that exceeded 120 mg MEDD.

As the CDC identified people who obtain multiple controlled substance prescriptions from multiple providers as one of the high-risk groups for opioid overdose, a summary of the total number of prescribers and pharmacies is shown in Table 4 for all Medi-Cal fee-for-service beneficiaries who had a paid claim for an opioid during that same year.

Table 4. Crosstabulation of Total Prescribers and Total Pharmacies for Opioid Paid Claims in the Medi-Cal Fee-For-Service Population (Dates of Service Between July 1, 2014, and June 30, 2015)

Total Utilizing Beneficiaries (n = 262,017)		Total Pharmacies					
		1	2	3	4	5 – 9	10+
Total Prescribers	1	208,071	8,131	886	129	24	0
	2	18,113	13,079	1,434	269	66	0
	3	2,952	3,104	1,467	288	113	0
	4	648	790	533	249	102	1
	5-9	300	403	365	241	208	7
	10+	2	5	3	5	22	7

The majority of these beneficiaries (n = 208,071; 79%) had only one paid claim for a prescription opioid medication during this one-year period. However, a total of 3,611 beneficiaries (1%) had paid claims for opioids from three or more prescribers and filled these claims at three or more pharmacies.

A total of 22,505 beneficiaries were included in an analysis of cumulative MEDD. Each of these beneficiaries was continuously eligible in the Medi-Cal fee-for-service program between January 1, 2015, and June 30, 2015, and had at least one paid claim for a prescription opioid medication between April 1, 2015, and June 30, 2015. This 90-day window was selected in order to identify the distribution of beneficiaries who exceeded a cumulative total of >120 mg MEDD for at least one of those days, and to identify beneficiaries who exceeded >120 mg MEDD for the entire 90 days, which would make this group at high-risk for overdose due to sustained high-dose opioid use over time.

As shown in Table 5, a total of 3,904 beneficiaries (17%) were identified in this group with at least one day out of 90 that exceeded >120 mg cumulative MEDD. Results are stratified by those who had a primary or secondary diagnosis of cancer and/or who were receiving hospice care, and those who did not have a primary or secondary diagnosis of cancer and no indication of hospice care in the medical claims data.

Table 5. Summary of Medi-Cal Fee-For-Service Beneficiaries Days >120 mg Cumulative MEDD (Dates of Service Between April 1, 2015, and June 30, 2015)

Days with MEDD >120 mg	Cancer/Hospice (n = 1,306)	Non-cancer/ Non-hospice (n = 21,199)	Total (n = 22,505)
0	1,078 (83%)	17,523 (83%)	18,601 (83%)
≥1	228 (17%)	3,676 (17%)	3,904 (17%)
≥2	225 (17%)	3,648 (17%)	3,873 (17%)
≥3	223 (17%)	3,593 (17%)	3,816 (17%)
≥10	217 (17%)	3,467 (16%)	3,684 (16%)
≥30	178 (14%)	2,778 (13%)	2,956 (13%)
≥60	120 (9%)	1,900 (9%)	2,020 (9%)
≥90	65 (5%)	963 (5%)	1,028 (5%)

Of the 1,028 beneficiaries that exceeded >120 mg cumulative MEDD for all 90 days, almost half (n = 410; 40%) had only one prescriber and one pharmacy for all opioid claims, while 49 beneficiaries (5%) had paid claims for opioids from three or more prescribers and filled these claims at three or more pharmacies. There was no statistically significant difference between the number of days that exceeded >120 mg cumulative MEDD when stratified by cancer/hospice status.

Conclusion/Discussion

While there is no completely safe dose of opioids, the ability to calculate morphine equivalent dose adds an additional assessment tool to combat potential opioid overdose and/or overuse. Federal and state agencies should provide guidelines and instructions for calculation of MEDD and promote case management and, as needed, referrals to appropriate pain specialists as higher doses of opioids are considered. Finally, all providers who prescribe opioids need to enroll in and access California's prescription drug monitoring program, CURES. In order to be most effective, MEDD calculations need to include all opioid prescriptions written for a patient, including those written by other providers.

Clinical Recommendations

- Review materials and resources for preventing prescription drug abuse available through the [California State Board of Pharmacy](#), [Medical Board of California](#), and the [California Department of Public Health](#).
- Weigh the benefits and risks of opioid therapy, especially for opioid therapy when alternative treatments are ineffective.
- Discuss with patients the risks and benefits of pain treatment options, including those that do not involve prescription painkillers.
- Follow best practices for responsible opioid prescribing, including:
 - Consult CURES initially and at every subsequent visit
 - Conduct a physical exam, urine drug test, and document pain history prior to prescribing opioids
 - Screen for substance abuse, mental health problems, and other physical conditions that are contraindicated for opioid use
 - Advise against concomitant use of alcohol, sedatives, and hypnotics
 - Implement pain treatment agreements

- Prescribe the lowest effective dose of short-acting opioid producing analgesia and improved function (no more than 80 mg MEDD) in a limited supply with no refills
- Regularly evaluate the role of opioid therapy beyond 3 months for non-cancer chronic pain
 - ❖ Use tapering (not abrupt cessation) to discontinue or reduce dose of opioids
- Track and document levels of pain and function at every visit
- Exercise vigilance at high doses
 - ❖ Consider prescribing naloxone as a rescue medication in the event of a potentially life-threatening overdose and instruct caregivers on proper use and administration. For detailed information on dosing and administration of naloxone, please go to the [Prescribe to Prevent](#) website
- Enroll in and access CURES reports to establish whether or not an individual is receiving controlled substances from multiple prescribers. The CURES report should be requested frequently for patients who are being treated for pain and/or addiction.

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Medi-Cal Drug Utilization Review (DUR) Program

Pauline Chan, R.Ph., MBA
Senior Pharmacist Consultant
Medi-Cal DUR Pharmacist
Pharmacy Policy Branch

12-14-2015

Medi-Cal DUR Program Overview

- Social Security Act Title XIX sec 1927 (g)(3)
- Also known as Omnibus Budget Reconciliation Act of 1990 (OBRA-90)
 - State shall provide, by no later than January 1, 1993, for a DUR program for covered outpatient drugs in order to ensure that prescriptions are:
 - Appropriate
 - Medically necessary
 - Not likely to result in adverse medical results



Medi-Cal DUR Program Overview - 2

- Medi-Cal DUR is a dynamic program designed to promote patient safety by optimizing beneficiaries' medical and pharmaceutical care
- Medi-Cal DUR serves the Fee-For-Service Population
- DUR is a two-phase process:
 - 1) Prospective DUR:
 - California's Medicaid Management Information System (CA-MMIS) includes an electronic screening process for all prescription drug claims that sends alerts to pharmacists when problems of therapeutic duplication, drug-disease or drug-allergy contraindications, incorrect dosage, and clinical misuse or abuse are identified
 - Future enhancements will make this decision-making process more interactive, in order to create an optimal environment to further engage pharmacies and providers



Medi-Cal DUR Program Overview - 3

2) Retrospective DUR:

- Includes continuous examination of claims data to identify quality-of-care issues, including patterns of fraud, abuse, gross overuse, or medically unnecessary care
- DUR publishes quarterly educational bulletins and ad-hoc educational alerts that include timely, evidence-based information for pharmacists and providers, enabling them to provide best possible care to beneficiaries
- DUR sends educational outreach letters to providers and pharmacies that target potential quality-of-care issues identified in educational bulletins



Medi-Cal DUR Program Overview - 4

- Ongoing dialogue among the DUR team guides the day-to-day work
- Xerox State Healthcare, LLC:
 - Daily claims processing
 - Provides integrated data system that supports both prospective and retrospective DUR
 - Dedicated staff includes a pharmacist and a physician
- UCSF School of Pharmacy:
 - Provides evidence-based drug therapy information, data analysis support, and technical writing
 - Dedicated staff includes a pharmacist and an epidemiologist



Medi-Cal DUR Board

- OBRA '90 also requires that state Medicaid programs maintain a Drug Utilization Review Board
 - Membership of the DUR board shall include professionals who have recognized knowledge and expertise in appropriate prescribing, dispensing and monitoring, evaluation, intervention and quality assurance
 - The Board serves in an advisory capacity and conducts four public forum meetings per year
 - DUR board members also serve on DHCS quality improvement project advisory panel and present at DHCS Learning Series



Medi-Cal DUR Annual Report

- Annual Report to Centers for Medicaid and Medicare Services (CMS)
 - CMS Medicaid Drug Utilization Review Annual Report
 - Each state is required to submit
 - Recent years with added focus on fraud, misuse and abuse & prescription drug monitoring system (CURES)
 - States' Innovative Practices to Improve Quality of Care
 - In 2013, CMS recognized 11 states with 13 innovative practices
 - California submitted 2 innovative practices
 - Educational intervention methodology
 - Improving psychotropic medication use
- Medi-Cal's DUR's innovative practices recognized by CMS



Additional References

CMS website:

<http://www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/prescription-drugs/drug-utilization-review.html>

Medi-Cal website:

http://files.medi-cal.ca.gov/pubsdoco/dur/DUR_about.asp

DHCS website:

<http://www.dhcs.ca.gov/services/Pages/PharmacyBenefits2.aspx>

CA Innovative Practices on CMS website:

<http://www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/prescription-drugs/downloads/dur-antipsychoticdrugmonitor.pdf>

<http://www.medicaid.gov/medicaid-chip-program-information/by-topics/benefits/prescription-drugs/downloads/dur-retrodur.pdf>



Questions?

Pauline.chan@dhcs.ca.gov





University of California
San Francisco

Morphine Equivalent Daily Dose to Prevent Opioid Overdose

Shal Lynch, PharmD, CGP
Health Sciences Associate Clinical Professor
Department of Clinical Pharmacy
School of Pharmacy

December 14, 2015

Drug Use Review (DUR) Bulletins

- Quarterly educational article
 - DHCS and DUR Board approve topics
 - Review current evidence-based guidelines
 - Include key points, clinical recommendations
 - Medi-Cal prescribing trends
 - Review/links to Medi-Cal policy
 - Collaborate with other state agencies, as appropriate
 - Disseminated via Medi-Cal Subscription Service and published on Medi-Cal website:

<http://files.medi-cal.ca.gov/pubsdoco/dur/edarticles.asp>

September 2015: DUR Educational Bulletin

Background

- Each day in the United States, 46 people die from an overdose of prescription opioid or narcotic pain relievers
- The CDC describes the following as risk factors for prescription opioid overdose
 - Multiple controlled substances Rxs from multiple providers
 - High daily doses of prescription painkillers
 - Low income / rural residence
 - Mental illness
 - History of substance abuse

September 2015: DUR Educational Bulletin 1

Morphine Equivalent Daily Dose (MEDD)

- Indicator of potential dose-related risk for adverse drug reactions to opioids, including overdose
- Used to assess comparative potency between opioids
- Should NOT be used to convert one opioid to another
- Calculation includes drug strength, quantity, days supply and a defined conversion factor
- Online converters (calculators) are available to assist clinicians
 - Links provided in bulletin

Drug Use Review (DUR) Bulletins

- Quarterly educational article
 - DHCS and DUR Board approve topics
 - Review current evidence-based guidelines
 - Include key points, clinical recommendations
 - Medi-Cal prescribing trends
 - Review/links to Medi-Cal policy
 - Collaborate with other state agencies, as appropriate
 - Disseminated via Medi-Cal Subscription Service and published on Medi-Cal website:
 - <http://files.medi-cal.ca.gov/pubsdoco/dur/edarticles.asp>

September 2015: DUR Educational Bulletin

Background

- Each day in the United States, 46 people die from an overdose of prescription opioid or narcotic pain relievers
- The CDC describes the following as risk factors for prescription opioid overdose
 - Multiple controlled substances Rxs from multiple providers
 - High daily doses of prescription painkillers
 - Low income / rural residence
 - Mental illness
 - History of substance abuse

September 2015: DUR Educational Bulletin 1

Morphine Equivalent Daily Dose (MEDD)

- Indicator of potential dose-related risk for adverse drug reactions to opioids, including overdose
- Used to assess comparative potency between opioids
- Should NOT be used to convert one opioid to another
- Calculation includes drug strength, quantity, days supply and a defined conversion factor
- Online converters (calculators) are available to assist clinicians
 - Links provided in bulletin

September 2015: DUR Educational Bulletin 2

Morphine Equivalent Daily Dose (MEDD)

- Patients receiving an MEDD of 100 mg or more had almost a nine-fold increased risk of overdose
- There is no completely safe opioid dose
- CDC data:
 - An estimated 80% of patients prescribed opioids receive < 100 mg MEDD from a single prescriber and account for 20% of overdoses
 - 10% of patients prescribed opioids receive > 100 mg MEDD from a single prescriber and account for 40% of overdoses
 - 10% of patients obtain opioids from multiple prescribers and account for 40% of overdoses

September 2015: DUR Educational Bulletin 3

Selected Organizations' MEDD Thresholds and Recommended Actions

Organization	MEDD Threshold (mg/day)	Recommended Action at MEDD Threshold
American Academy of Pain Medicine	>200	Increase frequency and intensity of monitoring
Utah State Clinical Guidelines	>120 – 200	Increase clinical vigilance
Veterans Affairs/Department of Defense	>200	Refer or consult
Washington State Agency Medical Directors' Group	>120	Consult from pain management expert
Canadian Guidelines	>200	Reassess or monitor
American College of Occupational and Environmental Medicine	≥50	Follow up frequently; document improved function
New York City Department of Health and Mental Hygiene	>100	Reassess pain status or consider other approaches
American Society of Interventional Pain Physicians	>91	Consider pain management consultation
Centers for Medicare and Medicaid Services	>120	Consider case management
Medical Board of California	≥80	Proceed cautiously and consider referral to specialist when higher doses are contemplated
California Division of Workers' Compensation	≥80	Increase clinical monitoring, consider specialty referral, attempt to wean to lower dose.

September 2015: DUR Educational Bulletin 4

State Medicaid Drug Use Review (DUR) Programs with Established Recommendations for MEDD or opioid dose limitation

State	MEDD Threshold (mg/day) or opioid dose limitation	Additional Information
Delaware	120	All long-acting opioids require prior authorization. The total dose for all narcotic therapy must be <120 mg MEDD.
Kansas	200	
Massachusetts	360	Individual dose limits for each opioid were determined based on utilization trends.
Maine	30	Prior authorization is required for any dose over 30mg; maximum allowable dose 300 mg
Michigan	30	
North Carolina	750	Maximum allowable dose
Oregon	120	
Washington	120	Based on State Agency Medical Directors' Group Guidelines
Wyoming	120	

September 2015: DUR Educational Bulletin 5

MEDD in the Medi-Cal Fee-for-Service Population

- Retrospective review of pharmacy claims, 7/1/14-6/30/15
- Medi-Cal pharmacy claims data were matched by NDC using the Morphine Equivalent Calculator Tool developed by the PDMP TTAC at Brandeis University (in collaboration with the CDC)
- MEDD was calculated for each claim
- The following equation was used to calculate MEDD:

$$\frac{(\text{Drug Strength}) \times (\text{Drug Quantity}) \times (\text{MME Conversion Factor})}{(\text{Days Supply})}$$

September 2015: DUR Educational Bulletin 6

Total Paid Claims Exceeding MEDD Thresholds (7/1/14-6/30/15)

	Recommended MEDD Thresholds		
	> 80 mg/day	> 100 mg/day	> 120 mg/day
Total paid claims (n=529,681)	71,236 (13.4%)	58,741 (11.1%)	47,769 (9.0%)
Total paid claims 14 day supply (n=237,106)	62,596 (26.4%)	54,060 (22.8%)	43,865 (18.5%)

- 87% of all paid claims < 80 mg MEDD
- 76% of claims for > 14 days supply < 80 mg MEDD

September 2015: DUR Educational Bulletin 7

Crosstabulation of Pharmacies and Prescribers for Paid Claims

Total Utilizing Beneficiaries (n=262,017)		Total Pharmacies					
		1	2	3	4	5-9	10+
Total Prescribers	1	208,071	8,131	886	129	24	0
	2	18,113	13,079	1,434	269	66	0
	3	2,952	3,104	1,467	288	113	0
	4	648	790	533	249	102	<10
	5-9	300	403	365	241	208	<10
	10+	<10	<10	<10	<10	22	<10

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Cumulative MEDD

- Continuously enrolled beneficiaries 1/1/15-6/30/15 with at least one paid claim for an opioid between 4/1/15-6/30/15 (n=22,505)
- 18,601 beneficiaries (83%) had 0 days with MEDD > 120 mg
- Of 1,028 beneficiaries with ≥ 90 days MEDD, 40% had one prescriber and one pharmacy

Days with MEDD > 120 mg	Cancer/Hospice (n=1,306)	Noncancer/Nonhospice (n=21,199)	Total (n=22,505)
≥ 30 days	178	2,778	2,956 (13%)
≥ 60 days	120	1,900	2,020 (9%)
≥ 90 days	65	963	1,028 (5%)

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Summary and Clinical Recommendations

- The ability to calculate morphine equivalent dose adds an additional assessment tool to combat potential opioid overdose
- Materials to prevent prescription drug abuse are available through a variety of sources (links provided in bulletin)
- Weigh the risks and benefits of pain treatment options, both prescription and nonprescription
- Follow best practices for opioid prescribing (summary in bulletin)
- Enroll in and access CURES reports

Randall S. Stafford, MD, PhD

Medi-Cal DUR Board Member

Professor of Medicine

Director, Program on Prevention Outcomes and Practices

Stanford Prevention Research Center

Stanford University School of Medicine



STANFORD PREVENTION
RESEARCH CENTER

the science of healthy living



Summary

- Medi-Cal DUR Program aligns with DHCS Quality Strategy & National Quality Strategy:
 - Triple Aim: Better Health, Better Care, Lower Cost
 - Focuses on patient safety and safe medication use
 - Measures patient outcome
- Medi-Cal DUR collaborates with other state organizations
 - State board of pharmacy
 - Medical Board of California
 - California Department of Public Health
 - California Department of Industrial Relations
- Future work includes use of academic detailing (AD) to further engage and educate Medi-Cal providers to optimize beneficiaries' medical and pharmaceutical care



Attachment 2

SPICE, BATH SALTS, AND BEHAVIORAL HEALTH

Spice (synthetic cannabinoids) and *bath salts* (synthetic cathinones) refer to two groups of designer drugs that have increased in popularity in recent years. These substances are created with *analogs* of commonly used illicit drugs. An analog is one of a group of chemical compounds that are similar in structure and pharmacology. This *Advisory* provides introductory information about spice and bath salts for behavioral health professionals who treat people with mental illness, substance use disorders, or both. It is not meant to present comprehensive information about spice or bath salts or treatment of substance use disorders involving their use. See the Resources section of this *Advisory* for links to additional information.

What Are Spice and Bath Salts?

Spice and bath salts are synthetic versions of controlled substances that are produced to avoid existing drug laws. In 2011, the U.S. Drug Enforcement Administration added, on a temporary, emergency basis, spice and bath salts analogs to its list of Schedule I substances. There are many synthetic chemicals that can be used to produce these drugs and their analogs; when federal or state regulations are amended to include new substance prohibitions, the makers of spice and bath salts turn to other synthetic analogs to produce these designer drugs. Both spice and bath salts are marketed online and sold in drug paraphernalia stores. They are attractively packaged and, to further help retailers evade the laws that prohibit possession or sale of designer drugs, may include labels that state “not for human consumption.”^{1,2}

Spice

Spice, also known as *herbal incense*, is dried, shredded plant material treated with a *cannabinoid* analog. Although labels on spice products will list the ingredients as “natural” psychoactive plant products, chemical analyses show that their active ingredients are primarily synthetic cannabinoids added to the plant material.² These synthetic analogs function similarly to the active ingredient in marijuana, Delta-9-tetrahydrocannabinol (Δ^9 -THC).

In this context, studies indicate that the synthetic cannabinoids act on the same receptors as natural cannabinoids, but they can bind with greater affinities and exhibit greater potency compared with natural cannabinoids.^{3,4} For example, many of the synthetic cannabinoids that have been found in spice are between 4 and 100 times more potent than Δ^9 -THC and produce correspondingly stronger psychoactive effects and side effects.³ These synthetics are known to alter various physiological processes, including neurotransmission and cardiovascular functioning, through the same signaling pathways as their natural counterparts.³ In addition, metabolites from some of these synthetic substances retain biologic activity and may account for a subset

Common Product Names for Spice

Arctic Synergy, Black Mamba, Bombay Blue, Cloud Nine, Genie, K2 Blonde, K2 Blueberry, Moon Rocks, Natures Organic, Skunk, Spice Diamond, Spice Gold, Spice Silver, Yucatan Fire, Zen, Zen Organic

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of the physiological changes associated with spice.⁴ It is also important to note that other psychoactive compounds may be added to spice (e.g., synthetic opioids have been found in spicelike blends), further amplifying and expanding its psychotropic effects.^{1,3}

Spice is marketed under more than 140 product names.⁵ Typically, it is smoked like marijuana⁶ or infused as a hot drink.² Spice is marketed as a “safer” alternative to marijuana and is not easily detected in urine or blood drug tests. Furthermore, the analogs that are added to produce the desired effects are constantly changing in response to federal regulations and state laws banning certain types of synthetic cannabinoids.^{4,7}

As a consequence, people who use these substances cannot know the precise array of chemicals that are in them or the serious, if not lethal, outcomes that may result from their use.^{1,8}

Bath salts

Bath salts, sometimes known as *plant food*, are usually produced as white, tan, or brown powders or crystals, but they are sometimes sold in tablets. Bath salts usually are ingested nasally as a powder, taken orally, injected, or smoked.⁹

Bath salts are synthetic cathinones. *Cathinone* is a naturally occurring substance found in the leaves of the *Catha edulis* plant, better known as *khat*. *Khat* is widely used for its stimulant effects, particularly in parts of Africa. Synthetic cathinones are derivatives of this

Common Product Names for Bath Salts

Bliss, Bloom, Blue Silk, Cloud Nine, Crazy Train, Drone, Energy-1, Hurricane Charlie, Ivory Wave, Lunar Wave, Ocean Snow, Purple Wave, Red Dove, Scarface, Snow Leopard, Stardust, Vanilla Sky, White Lightning, Zoom

compound and have effects similar to those of cocaine, amphetamine, or MDMA (3,4-methylenedioxy-N-methylamphetamine, or “ecstasy”).

Three of the most common compounds found in bath salts are mephedrone, methylone, and MDPV (3,4-methylenedioxypropylone). All three of these compounds have dopaminergic (among other) effects. Mephedrone appears to stimulate release of dopamine, whereas MDPV and methylone appear to increase dopamine levels by inhibiting dopamine reuptake.^{10,11,12} Synthetic cathinones have been found to increase dopamine levels equal to or more than those produced by the stimulant drugs they mimic.¹²

These three compounds are now illegal, but a wide range of other synthetic cathinones are now being used to create bath salts. Bath salts may contain any combination of unknown chemicals with unknown effects, making these substances more dangerous.¹³ In addition, the chemicals in bath salts are also often sold as ecstasy or other drugs, so they may be taken unintentionally.

Can People Become Dependent on Spice or Bath Salts?

People start using designer drugs for many of the same reasons people use other drugs—to experiment or because friends pressure them to use the drugs. Once they start using designer drugs, people may continue to use them to relieve stress, alleviate pain, function better, have fun, or cope with mental disorders.

Spice and dependence

Although there have been few studies to date on withdrawal and addiction liability, anecdotal evidence suggests that people who regularly use spice experience withdrawal and addiction symptoms.²

Bath salts and dependence

Both anecdotal and experimental evidence suggest that bath salts are highly addictive and produce an intense craving.¹⁴ One study of laboratory mice found that mephedrone achieved a brain stimulation reward similar to that achieved by cocaine, underscoring mephedrone's potential for abuse.¹⁵ A 2013 review article concluded that the increase in dopamine transmission created by the cathinones in bath salts likely creates a high potential for addiction.¹⁰

Who Uses Spice and Bath Salts?

Spice

Spice appears to be popular among young people. The 2012 Monitoring the Future (MTF) survey¹⁶ found that, aside from alcohol and tobacco, spice was the second most widely used substance among 10th and 12th graders, after marijuana; it was the third most widely used illicit drug among 8th graders, after marijuana and inhalants. The survey indicated that 11.3 percent of high school seniors, 8.8 percent of 10th graders, and 4.4 percent of 8th graders in the United States reported using spice in the past year.

The 2013 MTF survey¹⁷ reported that annual prevalence rates declined in all three grades, but the decline was significant only among 12th graders (7.9 percent annual prevalence, down from 11.3 percent). The 2013 rates for 10th and 8th graders were 7.4 percent and 4.0 percent, respectively.

Bath salts

Fewer young people use bath salts than use spice. The 2012 MTF survey¹⁶ found annual prevalence rates of 0.8 percent for grade 8, 0.6 percent for grade 10, and 1.3 percent for grade 12. Data from the 2013 MTF¹⁷ showed a slight increase in use in 8th and 10th grades (annual prevalence of 1.0 percent and 0.9, respectively) and some decline in 12th grade use (0.9 percent annual prevalence).

Calls to Poison Control Centers

Calls to U.S. poison control centers about spice increased from 2,906 in 2010 to 6,968 in 2011;¹⁸ they decreased to 5,230 in 2012 and to 2,663 in 2013.¹⁹

Bath salts-related calls to U.S. poison control centers increased dramatically between 2010 and 2011, from 304²⁰ to 6,137²¹ calls. Calls decreased to 2,691 in 2012 and to 996 in 2013.²¹

One investigation of 35 Michigan emergency department episodes involving adverse reactions to bath salts use found that, although people of all ages and both genders presented at the emergency department with symptoms related to bath salts use, 63 percent were ages 20 to 29, and 54 percent were male.²²

Included in the marketing of spice and bath salts are the claims that these products cannot be detected through routine drug screening. This makes these drugs popular with individuals who are subject to workplace or other mandatory drug testing (e.g., clients involved in drug court programs or otherwise in mandatory treatment, individuals on probation, members of the military). Although testing *is* available for some of the psychoactive compounds that have been found in spice and bath salts, these chemicals are typically not included in routine drug screens.

Is the Use of Spice or Bath Salts Related to Mental Disorders?

Spice

A growing body of evidence suggests an association between using spice and having an acute episode of psychosis in individuals with no history of psychosis or triggering a psychotic episode among individuals with a history of psychosis.^{23,24,25} However, current evidence has not established a definitive, causal link; additional research in this area is important.

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Marijuana contains the compound *cannabidiol*, which has antipsychotic properties. Spice, however, does *not* contain an analog for cannabidiol. That lack, combined with spice's high potency, appears to increase the risk of psychosis.²⁶

Evidence underscores the relationship between spice and other adverse psychoactive effects. For example, individuals who are intoxicated on spice can exhibit an array of cognitive changes (e.g., difficulty thinking clearly, confusion, amnesia), behavioral disturbances (e.g., agitation, restlessness, aggression), mood changes (e.g., anxiety, negative mood), or sensory and perceptual changes (e.g., paranoia, delusions, hallucinations).²⁷ Because spice use is relatively new, the long-term effects remain unknown.

Bath salts

Bath salts intoxication can produce symptoms that resemble those of mental disorders.²⁸ Symptoms include:^{5,28,29}

- Aggression and violent behavior.
- Confusion.
- Delirium.
- Delusions.
- Anxiety.
- Hallucinations.
- Panic attacks.
- Extreme paranoia.
- Acute psychosis.
- Agitation.

Adolescents and adults with mental illness are at greater risk of abusing drugs and developing a substance use disorder than are people without mental illness.³⁰ An investigation of emergency room episodes in Michigan found that 46 percent of the individuals who presented with bath salts intoxication were people with a history of mental illness (e.g., bipolar disorder, schizophrenia, depression).²²

What Are the Adverse Physical Effects of Spice and Bath Salts?

Spice

Spice can produce anticholinergic effects (dry mouth, dehydration), nausea, and seizures.⁵ Spice can also have cardiovascular effects, including tachycardia (rapid heart rate) and hypertension (increased blood pressure). In a few cases, the designer drug has been associated with heart attacks.² Because spice is a relatively new drug, it is not known whether it causes negative long-term physical effects.

Bath salts

Bath salts can also produce adverse physical effects, including hypertension, tachycardia, headaches, teeth grinding, overactive or overresponsive reflexes, nausea, vomiting, and seizures.⁵ As with ecstasy, there is heightened risk of hyperthermia and dehydration. In one study of emergency department episodes, the most commonly observed clinical symptom was tachycardia (56 percent).³¹ Less common clinical symptoms included twitching and other movement disorders (19 percent), hypertension (17 percent), and chest pain (17 percent).

What Are the Implications for Behavioral Health Services Providers?

It is likely that behavioral health services providers will encounter clients who use spice, bath salts, or both; practitioners should educate themselves about these substances and the ways in which they are advertised (see Resources).

Treatment for substance use disorders that involve the use of spice or bath salts does not differ significantly from treatment for substance use disorders that involve similar substances (e.g., marijuana or stimulants, respectively), although further research is needed.

However, there are a few substance-specific considerations, including assessment, education about the risks of use, and monitoring abstinence.

Assessment

Behavioral health services providers should include specific questions about spice and bath salts use when assessing clients at intake and periodically throughout treatment. Clients may not think to mention their use of these substances. Providers also need to remain mindful that clients sometimes switch from an initial drug of choice to spice or bath salts to avoid positive toxicology tests.

Because spice and bath salts can trigger psychosis or produce symptoms that resemble those of mental disorders, it is critical that practitioners provide careful assessment to distinguish between substance-induced symptoms and those of a preexisting mental illness.

Education about risk of use

Spice tends to be marketed as a natural, safe, and legal alternative to marijuana, and many individuals who use it believe those claims to be true. The 2013 MTF survey found that only 24 to 26 percent of 8th, 10th, and 12th grade students perceived “great risk” in using spice once or twice.¹⁷

Bath salts, although not marketed as natural botanical products, are marketed as legal alternatives to illicit substances. Consumers who use these substances may assume that “legal” means “safer.” For both spice and bath salts, it is important that behavioral health services providers offer specific education about the risks associated with use of these substances. Key points include the following:

- People who purchase spice or bath salts cannot know what psychoactive compounds or fillers were used to produce them. Products marketed with the same name may contain active ingredients different from or in addition to those stated on the packaging.

- The only “natural” ingredients in spice are the nonpsychoactive fillers. The psychoactive chemicals added to the fillers are synthetic, and they are much stronger than marijuana and carry higher risks of adverse effects, including psychosis.
- Spice and bath salts produce a wide range of both psychiatric and physical adverse effects that may be worse than those produced by the substances they mimic.
- The evidence suggests that spice and bath salts may be just as likely to produce addiction as the substances they mimic.

Monitoring abstinence

The compounds used in developing spice and bath salts are not typically included in routine toxicology screens. However, many laboratories have the capability to test for the most commonly used analogs in both spice and bath salts. Providers need to communicate with the laboratories they regularly use about providing testing for these substances.

As with marijuana, the commonly found compounds in spice have a long window of detection; one study reported the tested compounds to be detectable in urine for up to 102 days following self-reported cessation of use.³² For this reason, providers should monitor concentration levels over time rather than just the presence or absence of the compound.

Conclusion

Designer drugs are not new, and they are not a passing fad. Spice and bath salts are currently popular alternative drugs, but providers can expect that development of new psychoactive compounds specifically designed to evade substance regulations will continue, evolving as necessary to stay ahead of federal and state laws. Although substance use disorder treatment in instances where spice and bath salts are involved is not likely to vary from treatment involving similar substances, providers need to remain alert and informed to best help their clients.

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Resources

The DAWN Report: Drug-Related Emergency Department Visits Involving Synthetic Cannabinoids, Substance Abuse and Mental Health Services Administration

<http://www.samhsa.gov/data/2k12/DAWN105/SR105-synthetic-marijuana.pdf>

DrugFacts: Spice (“Synthetic Marijuana”), National Institute on Drug Abuse (NIDA)

<http://www.drugabuse.gov/publications/drugfacts/spice-synthetic-marijuana>

DrugFacts: Synthetic Cathinones (“Bath Salts”), NIDA

<http://www.drugabuse.gov/publications/drugfacts/synthetic-cathinones-bath-salts>

Drugs of Abuse, U.S. Drug Enforcement Administration (Spice, p. 62; Bath Salts, p. 74)

http://www.justice.gov/dea/pr/multimedia-library/publications/drug_of_abuse.pdf

NIDA’s Emerging Trends Web Page

<http://www.drugabuse.gov/drugs-abuse/emerging-trends>

Synthetic Drugs (factsheet), Office of National Drug Control Policy

http://www.whitehouse.gov/sites/default/files/page/files/synthetic_drugs_fact_sheet_455_2_15_12.pdf

Understanding the “Spice” Phenomenon, European Monitoring Centre for Drugs and Drug Addiction

<http://www.emcdda.europa.eu/publications/thematic-papers/spice>

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SAMHSA Advisory

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The DAWN Report

December 4, 2012

Drug-Related Emergency Department Visits Involving Synthetic Cannabinoids

Synthetic cannabinoids are substances that are designed to affect the body in a manner similar to marijuana but that are not derived from the marijuana plant.¹ Because they can be purchased with no age restrictions, their popularity among young people has grown.²

Synthetic cannabinoids are known by a variety of names, such as “Spice” or “K2,” and sometimes are referred to as “synthetic marijuana” or “fake marijuana” because they are marketed with claims that their effects mimic those of marijuana. Synthetic cannabinoids are typically sprayed onto herbal products, many of which are listed as inactive on the product packaging.²

Although certain synthetic cannabinoids and/or specific chemicals contained in these preparations were made illegal in some States, a comprehensive national ban was not enacted until July 2012.³ Therefore, products containing synthetic cannabinoids were frequently marketed as “legal” and “not for human consumption” and could be purchased online and in legal retail outlets such as convenience stores.¹

Because products marketed as synthetic cannabinoids contain different ingredients from each other, it is difficult to identify which physical effects are caused by synthetic cannabinoids.⁴ They have been reported to cause agitation, anxiety, nausea, vomiting, tachycardia, elevated blood pressure, tremor, seizures, hallucinations, paranoid behavior, and nonresponsiveness.^{2,5} These products are relatively new, and related clinical and public health outcomes have not been fully examined. Synthetic cannabinoids are not currently identified using routine screening tests, and the creation of new products of this type makes it difficult to detect these chemicals or regulate these products.

The Drug Abuse Warning Network (DAWN) first detected a measurable number of emergency department (ED) visits involving synthetic cannabinoids in 2010, and this report presents data related to these visits.⁶ DAWN is a public health surveillance system that monitors drug-related ED visits in the United States. To be a DAWN



IN BRIEF

In 2010, an estimated 11,406 emergency department (ED) visits involved a synthetic cannabinoid product, sometimes referred to as “synthetic marijuana” and commonly known by street names such as “Spice” or “K2”

Three fourths of these ED visits involved patients aged 12 to 29 (75 percent), of which 78 percent were male

The majority (76 percent) of these ED visits did not receive follow-up care upon discharge from the ED

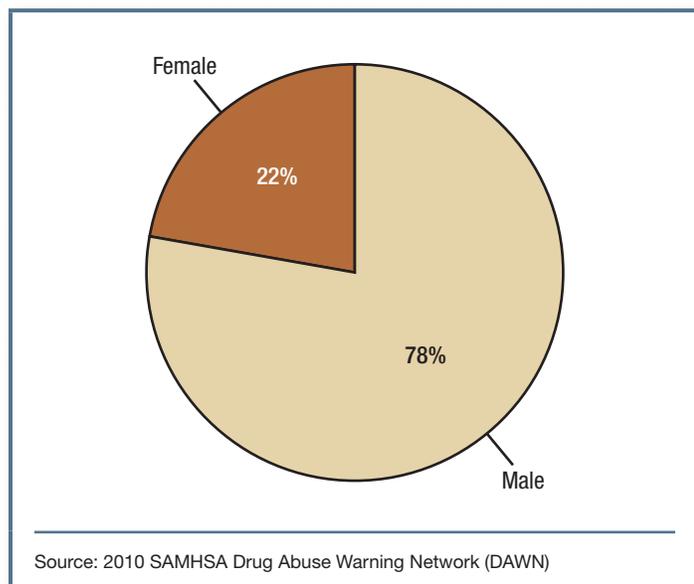
case, an ED visit must have involved a drug, either as the direct cause of the visit or as a contributing factor.

Of the approximately 2,300,000 ED visits that involved drug misuse or abuse in 2010, synthetic cannabinoids were specifically linked to an estimated 11,406 visits. This issue of *The DAWN Report* examines ED visits involving synthetic cannabinoid products in 2010 among patients aged 12 to 29. The report focuses on this age group because ED visits involving synthetic cannabinoids are concentrated in this age range (8,557 visits, or 75 percent of all visits involving synthetic cannabinoids, were made by patients aged 12 to 29 in 2010).

Gender and Age

For patients aged 12 to 29, males made more than three quarters (78 percent) of ED visits involving synthetic cannabinoids in 2010 (Figure 1). The rates of visits per 100,000 population for patients aged 12 to 17, 18 to 20, and 21 to 24 were similar (14.9, 13.9, and 11.8 visits per 100,000 population, respectively) (Table 1). However, the rate for those aged 25 to 29 (4.1 visits per 100,000 population) was lower than those for patients aged 12 to 17 (14.9 visits per 100,000 population) and those aged 18 to 20 (13.9 visits per 100,000 population).

Figure 1. Emergency Department (ED) Visits Involving Synthetic Cannabinoids among Patients Aged 12 to 29, by Gender: 2010



Drug Combinations

In the majority (59 percent) of ED visits involving synthetic cannabinoids for patients aged 12 to 29, no other substances were involved (Figure 2). This differs from ED visits involving other illicit drugs or nonmedical use of pharmaceuticals, in which the majority of visits involved multiple drugs.⁷ Synthetic cannabinoids were used in combination with one other substance in 36 percent of visits related to their use, but were rarely used in combination with two or more substances (6 percent). The types of drugs most frequently used in combination with synthetic cannabinoids were marijuana (17 percent), pharmaceuticals (17 percent), and alcohol (13 percent).

Disposition of ED Visits

Among ED visits involving synthetic cannabinoids made by patients aged 12 to 29 in 2010, it appears that the majority (76 percent) did not receive follow-up care (admission to the hospital, transfer to another health care facility, or referral to a detoxification/treatment program). Most of the 2,077 visits resulting in follow-up care involved synthetic cannabinoids in combination with other substances (75 percent).

Table 1. Emergency Department (ED) Visits Involving Synthetic Cannabinoids among Patients Aged 12 to 29, by Age Group: 2010

Age Group	Estimated Number of ED Visits	Rate per 100,000 Population*
Total, Aged 12 to 29	8,557	11.1
Aged 12 to 17	3,780	14.9
Aged 18 to 20	1,881	13.9
Aged 21 to 24	2,022	11.8
Aged 25 to 29	873	4.1

* Rates take into consideration the population size of each group; therefore, groups of different sizes may have varying numbers of ED visits but have similar population rates.

Source: 2010 SAMHSA Drug Abuse Warning Network (DAWN).

Synthetic Cannabinoids Compared with Marijuana-Related ED Visits

Because synthetic cannabinoids have been marketed as a legal alternative to marijuana, this section will provide a brief comparison of the patient characteristics of ED visits between marijuana and synthetic cannabinoids. Marijuana-related ED visits outnumber synthetic cannabinoid-related visits (461,028 vs. 11,406 visits). The average patient age for marijuana-related visits was 30 years and the average patient age for synthetic cannabinoid-related visits was 24 years. The age distribution also differed between the two drugs. Synthetic cannabinoid-related visits were concentrated in the younger age groups: 75 percent of the visits involved patients aged 12 to 29, with 33 percent of the patients aged 12 to 17. In comparison, 58 percent of marijuana-related visits involved patients aged 12 to 29, with 12 percent in the 12 to 17 age group (Figure 3).

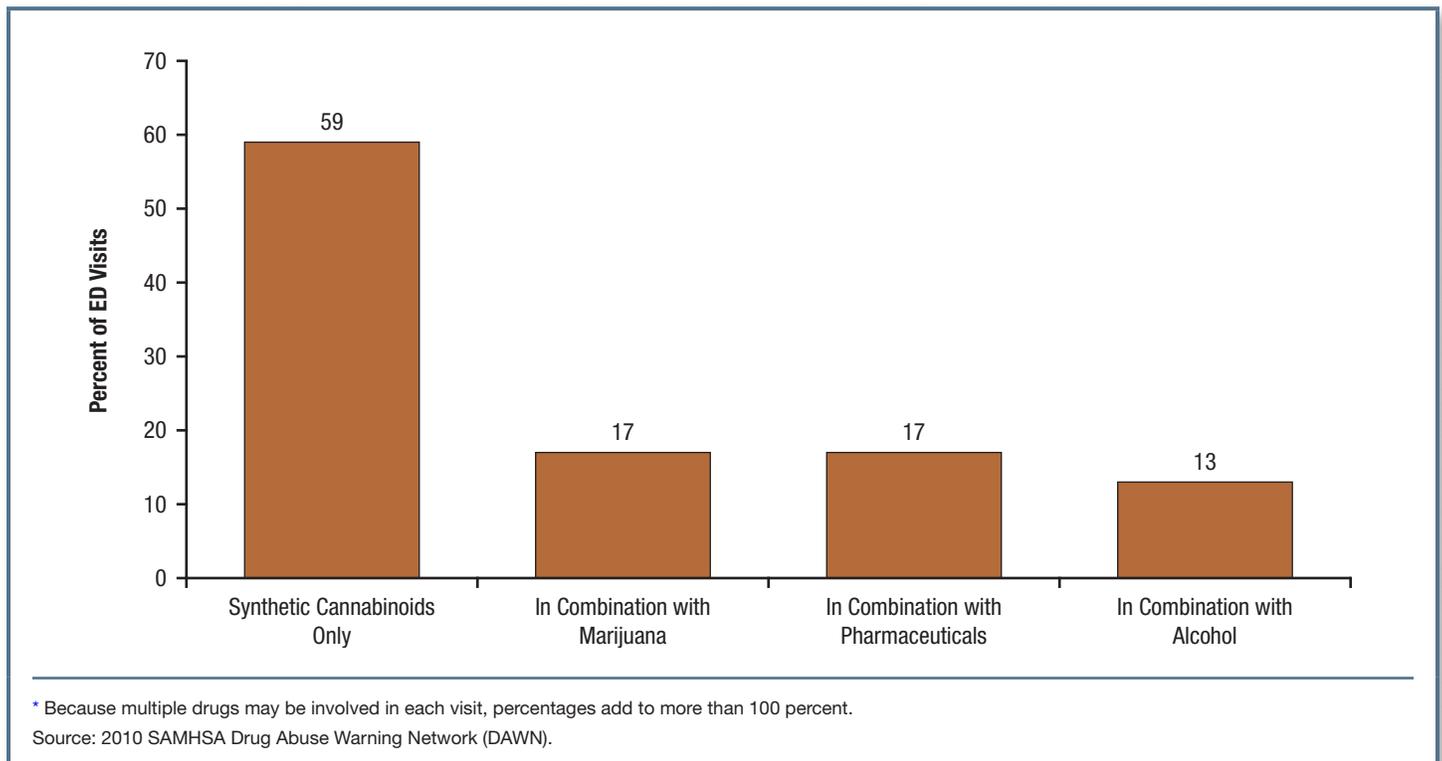
When patients in the 12 to 29 age range were compared, synthetic cannabinoid-related ED visits

were more likely to involve male patients than were marijuana-related visits (78 vs. 66 percent) (Figure 4). Further, synthetic cannabinoids were more likely to be the only drug implicated in the visit, whereas marijuana was more frequently combined with other drugs (59 vs. 31 percent, respectively; data not shown).

Discussion

As synthetic cannabinoids have become more available, the number of ED visits involving synthetic cannabinoids has increased. The higher proportion of ED visits in younger age groups, especially in patients aged 12 to 17, combined with results from a national survey of high school seniors revealing that 11 percent reported using “synthetic marijuana” in 2011, is cause for concern.⁸ Because it is difficult to regulate these products that are easily available online, synthetic cannabinoids may be more accessible to young people than marijuana.⁹ Educators can help prevent use of synthetic cannabinoids by addressing use of these

Figure 2. Emergency Department (ED) Visits Involving Synthetic Cannabinoids Only or in Combination with Other Substances* among Patients Aged 12 to 29: 2010



substances in programs designed to prevent use of illicit drugs. Parents can also discuss the dangers of these drugs with their children and use parental controls for online purchases.

Because of limited availability of tests for synthetic cannabinoids, data collection efforts in the ED may have missed visits in which they were involved. However, even in the absence of positive drug test results, health care providers can remain alert to symptoms that may be attributed to synthetic cannabinoids and, when appropriate, inquire about their use.⁴ Further monitoring will be necessary to determine whether synthetic cannabinoid-related health problems continue to be reported. This monitoring can help improve awareness among health care professionals of the possible adverse health effects of these substances. Because most synthetic cannabinoid-related ED visits result in discharge from the ED, a patient's time in the ED is a valuable opportunity for intervention and education.

Figure 4. Emergency Department (ED) Visits Involving Synthetic Cannabinoids Compared with Visits Involving Marijuana among Patients Aged 12 to 29, by Gender*: 2010

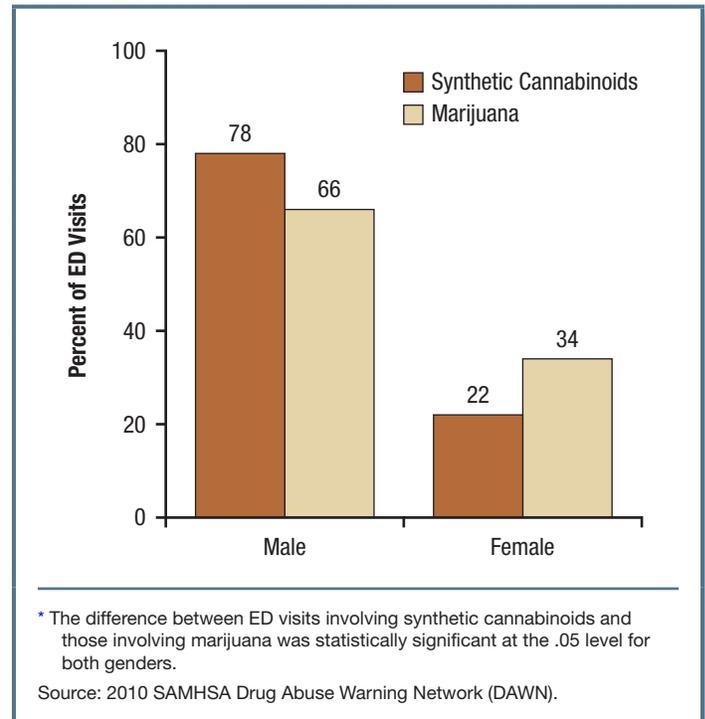
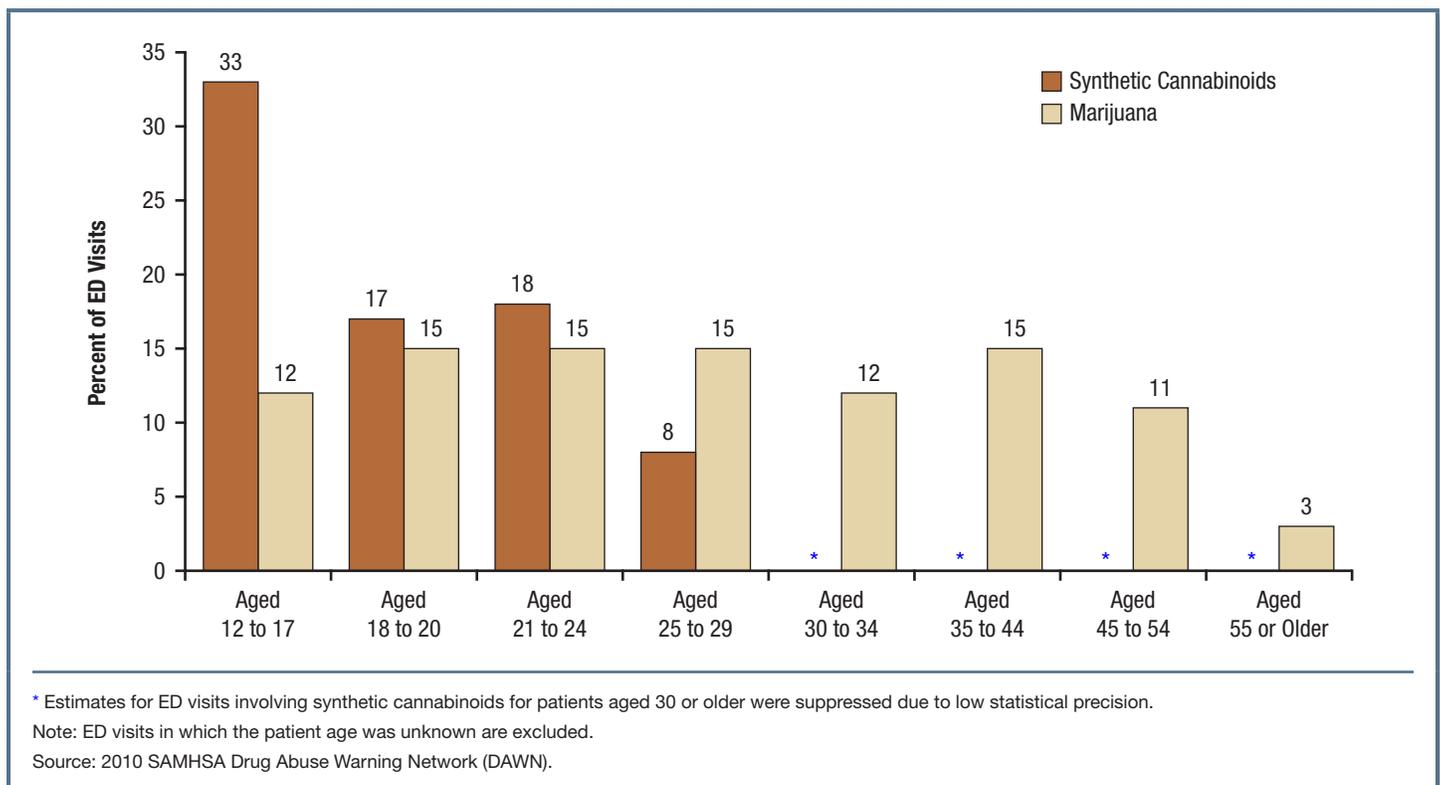


Figure 3. Age Distribution of Synthetic Cannabinoid and Marijuana-Related Emergency Department (ED) Visits: 2010



End Notes

1. Office of National Drug Control Policy. (2012). *Fact Sheet: Synthetic drugs (a.k.a. K2, Spice, bath salts, etc.)*. Retrieved from <http://www.whitehouse.gov/ondcp/ondcp-fact-sheets/synthetic-drugs-k2-spice-bath-salts>
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5. Fattore, L., & Fratta, W. (2011). Beyond THC: The new generation of cannabinoid designer drugs. *Frontiers in Behavioral Neuroscience*, 5(60), 1-12.
6. Synthetic cannabinoids were reported to DAWN under the following names: Spice, K2, K2 Incense, K2 Joint, K2 Spice, K2 Spice Incense, K2 Summit, K2 Synthetic Marijuana, Black Mamba, Blaze Incense, Cloud 9, Damiana Leaf, JWH-018, JWH-250, Serenity Now Herbal Incense, Spike99 Ultra, Synthetic Cannabis, Synthetic Marijuana, and Wicked XXX Herbal Incense.
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Suggested Citation

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The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related morbidity and mortality. DAWN uses a probability sample of hospitals to produce estimates of drug-related emergency department (ED) visits for the United States and selected metropolitan areas annually. DAWN also produces annual profiles of drug-related deaths reviewed by medical examiners or coroners in selected metropolitan areas and States.

Any ED visit related to recent drug use is included in DAWN. All types of drugs—licit and illicit—are covered. Alcohol involvement is documented for patients of all ages if it occurs with another drug. Alcohol is considered an illicit drug for minors and is documented even if no other drug is involved. The classification of drugs used in DAWN is derived from the Multum *Lexicon*, copyright 2010 Lexi-Comp, Inc., and/or Cerner Multum, Inc. The Multum Licensing Agreement governing use of the *Lexicon* can be found at <http://www.samhsa.gov/data/DAWN.aspx>.

DAWN is one of three major surveys conducted by the Substance Abuse and Mental Health Services Administration's Center for Behavioral Health Statistics and Quality (SAMHSA/CBHSQ). For more information on other CBHSQ surveys, go to <http://www.samhsa.gov/data/>. SAMHSA has contracts with Westat (Rockville, MD) and RTI International (Research Triangle Park, NC) to operate the DAWN system and produce publications.

For publications and additional information about DAWN, go to <http://www.samhsa.gov/data/DAWN.aspx>.



U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Substance Abuse & Mental Health Services Administration
Center for Behavioral Health Statistics and Quality
www.samhsa.gov/data

The CBHSQ Report

Short Report

October 16, 2014

UPDATE: DRUG-RELATED EMERGENCY DEPARTMENT VISITS INVOLVING SYNTHETIC CANNABINOIDS

AUTHORS

Donna M. Bush, Ph.D., F-ABFT and David A. Woodwell, M.P.H.

INTRODUCTION

Synthetic cannabinoids are manmade chemicals that are applied (often dissolved in a solvent and sprayed) onto plant material that is not marijuana, marketed as herbal incense products and also as a “legal high.”¹ These herbal products were originally available in 2004 in several European countries with brand names “Spice,” “Spice Diamond,” “Spice Gold,” and “Yucatan Fire.”² By late 2008, synthetic cannabinoids were identified in the United States in “Spice Diamond” and “Spice Artic Energy” products.³ Even though the caution “not for human consumption” is prominently printed on the packaging, these products are used by those seeking a legal high, with smoking as the most common route of administration.^{1,4} They are labeled “not for human consumption” to mask their intended purpose and avoid Food and Drug Administration (FDA) regulatory oversight of the manufacturing process.¹ Users claim that synthetic cannabinoids mimic the effects of delta-9-tetrahydrocannabinol (THC), the primary psychoactive ingredient in marijuana.¹

There is an incorrect assumption that synthetic cannabinoids are safe.⁴ Synthetic cannabinoids produce a combination of adverse effects that resemble intoxication from delta-9-tetrahydrocannabinol (delta-9-THC), the psychoactive component of marijuana. However, synthetic cannabinoids appear to be more potent and may stay active in the body longer than delta-9-THC.⁵ The adverse effects of synthetic cannabinoids include severe agitation, anxiety, nausea, vomiting, tachycardia (racing heartbeat), elevated blood pressure, tremors, seizures, hallucinations, paranoid behavior, and nonresponsiveness.^{1,5} After regular consumption, withdrawal signs and symptoms have been observed.⁶ Death after use of synthetic cannabinoids has also been reported.^{4,7}

Because products marketed as synthetic cannabinoids (e.g., “Spice,” “K2,” and hundreds of exotic brand names) contain various amounts of different ingredients or combinations that are different from each other, it is difficult to identify which adverse effects are caused by which synthetic cannabinoid chemicals.^{4,5,8} Additionally, it appears that the chemical structures of the psychoactive components of these products, as well as the composition of the herbal products themselves, is continually changing. There are also unpredictable contaminants in these products since they are manufactured illicitly.^{4,5} Concern about the availability and use of these products has continued to increase, as they are easily purchased online and in small retail outlets, such as “head shops” and convenience stores, without age restrictions.^{1,5}

The U.S. Drug Enforcement Administration (DEA) and nearly all states have taken some degree of regulatory control over synthetic cannabinoids as they are identified.^{4,9} Manufacturers of these compounds have modified their chemical structures, sometimes only very slightly, to evade current laws and regulations to be able to continue marketing these products as “legal highs.”⁴ The ingredients are rarely clearly labeled on the packaging, and the brand names vary widely. Over the past 5 years, the DEA has identified more than 200 designer drugs, many of which are synthetic cannabinoids manufactured in China.¹⁰ Designer drugs are drugs synthesized to be chemically and pharmacologically similar to illicit drugs in order to avoid DEA scrutiny. A list of 27 synthetic cannabinoid chemicals identified in substances secured in law enforcement operations and analyzed by federal, state, and local forensic laboratories was published in a 2014 National Forensic Laboratory Information System (NFLIS)



In Brief

- The number of emergency department (ED) visits involving synthetic cannabinoids increased significantly from 11,406 visits in 2010 to 28,531 visits in 2011.
- The number of ED visits involving synthetic cannabinoids for patients aged 12 to 17 doubled from 3,780 visits in 2010 to 7,584 visits in 2011; for patients aged 18 to 20, visits increased fourfold from 1,881 visits in 2010 to 8,212 visits in 2011.
- Males accounted for about 79 percent (19,923 visits) of the 28,531 ED visits in 2011 involving synthetic cannabinoids; 2011 DAWN estimates indicate a threefold increase in synthetic cannabinoid-related ED visits for females.
- In 2011, synthetic cannabinoids were the only substances involved in about two-thirds of the synthetic cannabinoid-related ED visits for patients aged 12 to 20 years; for those aged 21 or older, almost half of the synthetic cannabinoid-related ED visits involved only those drugs.

Special Report.¹¹ This special report shows that the synthetic cannabinoid chemicals identified in laboratory reports from 2010 are vastly different from those chemicals identified in 2013. Moreover, the availability of synthetic cannabinoids has surged since 2010, as indicated by the number of laboratory reports issued in January through June in 2010 (469) compared to January through June in 2013 (17,241).¹¹ As of June 2014, a number of synthetic cannabinoid chemicals have been either temporarily or permanently placed in Schedule I under the Controlled Substances Act, indicating that these are drugs with no currently accepted medical use and a high potential for abuse.¹¹ Schedule I drugs are among the most dangerous, with the potential for severe psychological or physical dependence.

Public health concerns remain heightened because synthetic cannabinoids have evolved and increased in number over time, even as regulatory action has been taken to ban specifically identified chemicals. The Centers for Disease Control and Prevention (CDC) investigated two severe illness outbreaks in 2013 that were linked to the use of synthetic cannabinoids.^{12,13} The Colorado Department of Public Health and Environment, with the assistance of the CDC, investigated 221 hospital emergency department (ED) reports of severe illness due to ingestion of synthetic cannabinoids.⁴ CDC also reported acute kidney injury associated with the use of synthetic cannabinoids in multiple states.¹⁴

Even with ongoing regulatory action and enforcement, these products continue to be marketed widely, especially to adolescents and those seeking a legal high with a desire to evade detection by current drug testing technologies.⁴ Synthetic cannabinoids are not currently identified using routine screening tests, and the creation of new synthetic cannabinoid chemicals makes it difficult to detect them in analysis of bodily fluids (e.g., blood, serum, urine).^{4,8,15,16}

The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitored drug-related ED visits in the United States. To be a DAWN case, an ED visit must have involved a drug, either as the direct cause of the visit or as a contributing factor. DAWN first detected a measurable number of ED visits involving synthetic cannabinoids in 2010, and a report was published in 2012.^{17, 18} This report presents updated data for 2011 as well as trends between 2010 and 2011.

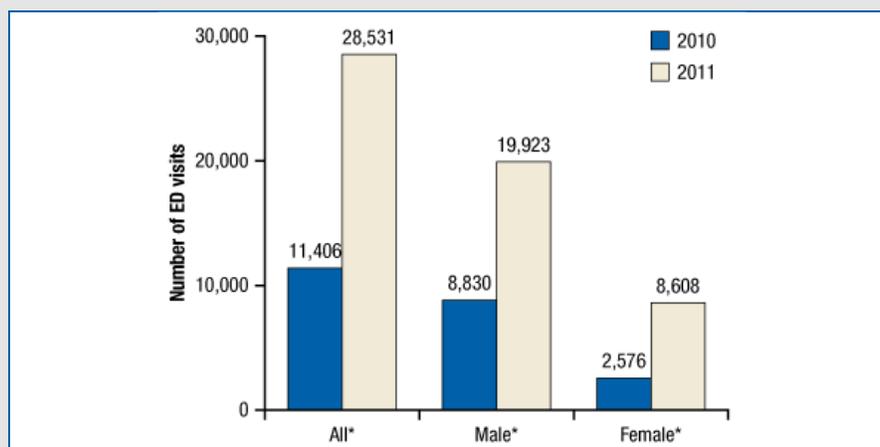
OVERVIEW

Of the approximately 2,460,000 ED visits that involved drug misuse or abuse in 2011, synthetic cannabinoids were specifically linked to an estimated 28,531 ED visits. This was a statistically significant increase from 2010, when 11,406 visits occurred (Figure 1).

TRENDS IN ED VISITS BY GENDER AND AGE

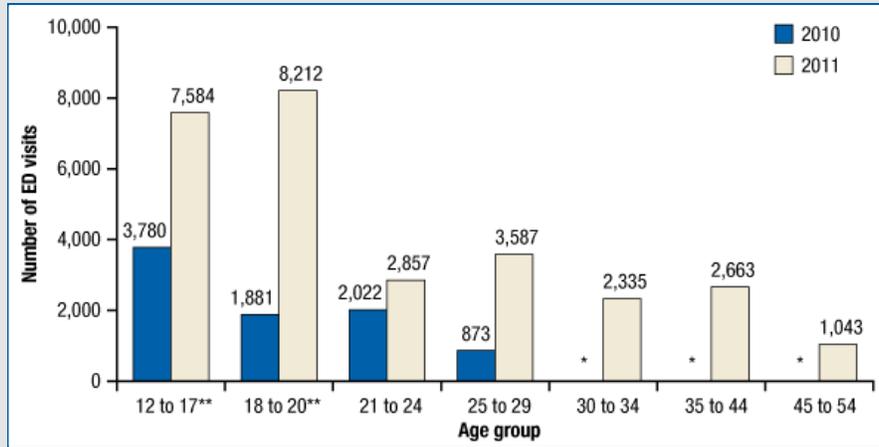
From 2010 to 2011, there were statistically significant increases for both males and females in the number of ED visits involving synthetic cannabinoids. For male patients, ED visits increased significantly from an estimated 8,830 visits in 2010 to an estimated 19,923 visits in 2011 (Figure 1). Visits for female patients tripled from 2,576 visits in 2010 to 8,608 visits in 2011.

Figure 1. Emergency department (ED) visits involving synthetic cannabinoids, by gender: 2010 and 2011



* The difference between 2010 and 2011 was statistically significant at the .05 level.
Source: 2011 SAMHSA Drug Abuse Warning Network (DAWN).

Figure 2. Emergency department (ED) visits involving synthetic cannabinoids, by age group: 2010 and 2011



* Low precision; no estimate reported.

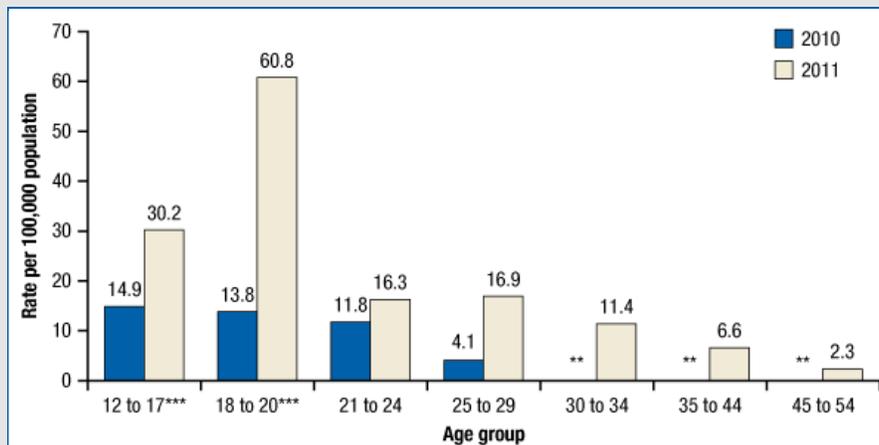
** The difference between 2010 and 2011 was statistically significant at the .05 level.

Source: 2010 and 2011 SAMHSA Drug Abuse Warning Network (DAWN).

When looking at visits made to the ED involving synthetic cannabinoids by age, the number of visits for patients aged 12 to 17 had a statistically significant doubling from 3,780 visits in 2010 to 7,584 visits in 2011 (Figure 2). For patients aged 18 to 20, visits increased fourfold, from 1,881 visits in 2010 to 8,212 visits in 2011. Although the number of visits appears to have increased for patients aged 21 to 24 and aged 25 to 29 between 2010 and 2011, the difference was not statistically significant. For older age groups, 2011 was the first year that visits involving synthetic cannabinoids reached a measurable level. There were 2,335 ED visits involving synthetic cannabinoids by patients aged 30 to 34, 2,663 visits made by patients 35 to 44, and 1,043 visits made by patients aged 45 to 54 (Figure 2).

The rate of ED visits involving synthetic cannabinoids per 100,000 population was calculated in order to compare age groups of different sizes. In 2011, the rate was highest among persons aged 18 to 20, with 60.8 visits per 100,000 population (Figure 3).

Figure 3. Emergency department (ED) visits involving synthetic cannabinoids, rate per 100,000 population,* by age group: 2010 and 2011



* Rates take into consideration the population size of each group; therefore, groups of different sizes may have varying numbers of ED visits but have similar population rates.

** Low precision; no estimate reported.

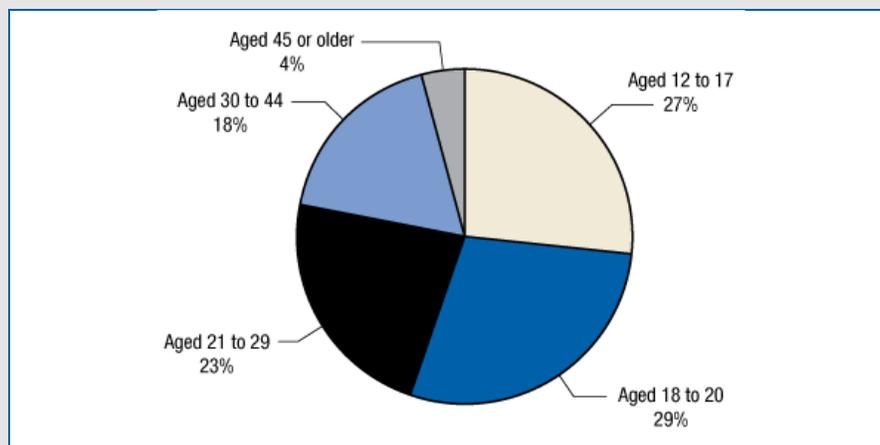
*** The difference between 2010 and 2011 was statistically significant at the .05 level.

Source: 2010 and 2011 SAMHSA Drug Abuse Warning Network (DAWN).

This rate was double the rate among persons aged 12 to 17 (30.2 visits per 100,000 population) and higher than the rate among persons aged 21 or older. Between 2010 and 2011, the rate of ED visits involving synthetic cannabinoids had a statistically significant doubling for patients aged 12 to 17, from 14.9 visits per 100,000 population in 2010 to 30.2 visits per 100,000 population in 2011. The rate per 100,000 population for those aged 18 to 20 had a statistically significant increase of more than four times, from 13.8 visits per 100,000 population in 2010 to 60.8 visits per 100,000 population in 2011. The rate of ED visits involving synthetic cannabinoids did not increase significantly for patients aged 21 or older (Figure 3).

The age distribution of the estimated 28,531 ED visits involving synthetic cannabinoids in 2011 is shown in Figure 4. Approximately a quarter of all visits were made by patients aged 12 to 17 (7,584 visits, or 27 percent), and 29 percent of visits were made by patients aged 18 to 20 (8,212). Summed together, patients aged 12 to 20 made 55 percent (15,796 visits) of all ED visits involving synthetic cannabinoids in 2011. An additional 41 percent of ED visits involving synthetic cannabinoids were made by patients aged 21 to 44. The remaining 4 percent of visits were made by those aged 45 or older (1,090 visits).

Figure 4. Emergency department (ED) visits involving synthetic cannabinoids, by age group*: 2011



*Percentages may not sum to 100 due to rounding.

Source: 2010 and 2011 SAMHSA Drug Abuse Warning Network (DAWN).

DRUGS INVOLVED IN ED VISITS

Among patients aged 20 or younger, no other substances were combined with synthetic cannabinoids in about two-thirds (65 percent) of ED visits related to their use; among patients aged 21 or older, 47 percent of visits involved synthetic cannabinoids only (Table 1).

Table 1. Emergency department (ED) visits involving synthetic cannabinoids only or in combination with other substances, by age group: 2011

Drug combination	Aged 20 or younger		Aged 21 or older	
	Number of ED visits*	Percent of ED visits*	Number of ED visits*	Percent of ED visits*
Total	15,998	100	12,533	100
Synthetic cannabinoids only	10,335	65	5,886	47
Synthetic cannabinoids in combination	5,664	35	6,646	53
Illicit drugs	3,404	21	3,335	27
Other marijuana	2,708	17	**	**
Stimulants***	**	**	1,018	8
Pharmaceuticals	2,531	16	3,243	26
Alcohol	2,438	15	1,368	11

*Because multiple drugs may be involved in each visit, estimates of visits by drug may add to more than the total, and percentages may add to more than 100 percent.

** Low precision; no estimate reported.

*** Includes amphetamines and methamphetamine.

Source: 2011 SAMHSA Drug Abuse Warning Network (DAWN).

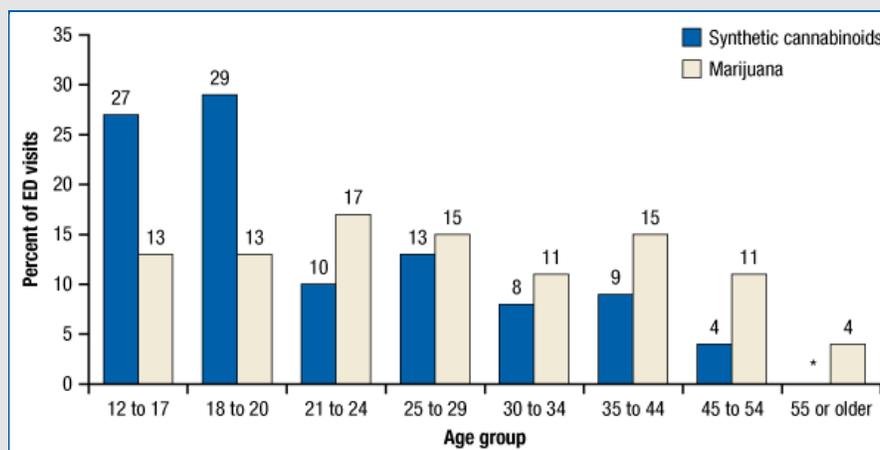
Synthetic cannabinoids were combined with illicit drugs in 21 percent of visits among patients aged 20 or younger and in 27 percent of visits among patients aged 21 or older.

In 2011, synthetic cannabinoids were combined with pharmaceuticals in 16 percent of visits among patients aged 12 to 20 and in 26 percent of visits among patients aged 21 or older.

SYNTHETIC CANNABINOIDS COMPARED WITH MARIJUANA-RELATED ED VISITS

Because synthetic cannabinoids have been marketed as a legal alternative to marijuana, this section will provide a brief comparison of the patient characteristics between ED visits for marijuana and those for synthetic cannabinoids. In 2011, marijuana-related ED visits outnumbered synthetic cannabinoid-related visits (455,668 and 28,531 visits, respectively). The average patient age for marijuana-related visits was 30 years of age, and the average patient age for synthetic cannabinoid-related visits was 23 years of age (data not shown). The age distribution also differed between the two drugs (Figure 5). More than half of synthetic cannabinoid-related visits (55 percent) were made by patients aged 12 to 20, with 27 percent aged 12 to 17. In comparison, 26 percent of marijuana-related visits involved patients aged 12 to 20, with 13 percent aged 12 to 17.

Figure 5. Age distribution of synthetic cannabinoid and marijuana-related emergency department (ED) visits: 2011



* Low precision; no estimate reported.

Source: 2011 SAMHSA Drug Abuse Warning Network (DAWN).

DISPOSITION OF ED VISITS

Among the 28,531 ED visits involving synthetic cannabinoids in 2011, about 3,510 (12 percent) resulted in admission to the hospital or transfer to another health care facility (Table 2).

Table 2. Disposition of emergency department (ED) visits involving synthetic cannabinoids, by age group: 2011

Drug combination	Treated and released		Admitted or transferred	
	Number of ED visits	Percent of ED visits	Number of ED visits	Percent of ED visits
Total ED visits	22,938	100	3,510	100
Aged 12 to 17	6,824	30	745	21
Aged 18 to 20	6,547	29	822*	23*
Aged 21 to 29	4,948	22	702	20
Aged 30 to 44	3,792	17	777	22
Aged 45 or older	**	**	**	**

*Estimate may be unreliable due to low precision.

**Low precision; no estimate reported.

Source: 2011 SAMHSA Drug Abuse Warning Network (DAWN).

Among patients who were admitted or transferred, 21 percent were aged 12 to 17, and 23 percent were aged 18 to 20. Patients aged 21 to 29 and those aged 30 to 44 each made up about one-fifth of visits resulting in admission or transfer (20 and 22 percent, respectively). Of patients that received follow-up care (e.g., patients who were referred to detoxification/treatment, admitted to the hospital (any unit), or transferred), approximately one-half involved synthetic cannabinoids only and no other substance (54 percent; data not shown).

DISCUSSION

As synthetic cannabinoids have become more available, the estimated number of ED visits involving synthetic cannabinoids has increased threefold from 2010 to 2011.¹⁹ Most of the estimated 28,531 ED visits in 2011 involving synthetic cannabinoids were made by males (79 percent). This is consistent with information published in a summarized review of adverse events, medical treatments and outcomes.²⁰ Additionally, 2011 DAWN data indicate a threefold increase in ED visits made by females compared to 2010.

For those aged 12 to 17, the rates of ED visits involving synthetic cannabinoids more than doubled from 14.9 per 100,000 in 2010 to 30.2 per 100,000 in 2011. For patients aged 18 to 20, the rates of ED visits involving synthetic cannabinoids increased more than fourfold from 13.8 per 100,000 in 2010 to 60.8 per 100,000 in 2011. These significant increases in rates of ED visits involving synthetic cannabinoids, especially among adolescents, are of great concern to health care professionals, public health officials, and law enforcement.^{4,5} To date, only acute adverse effects of synthetic cannabinoid use have been reported. There is little information about the health effects and toxicity following chronic use of synthetic cannabinoids, but several cases of new-onset psychosis after multiple uses of synthetic cannabinoids have recently been reported.^{5,21}

Concern is not limited to synthetic cannabinoid use by adolescents and young adults. The substantial number of ED visits involving synthetic cannabinoids in 2011 allowed for statistical analysis and reporting of patients in more age ranges, including patients in the 45 to 54 age range. Reports in scientific literature indicate a wider appeal of synthetic cannabinoids among those not only seeking what is advertised as a legal high, but also by those in parole and probation situations and by those in workplaces that require drug testing.^{4,5,15} This may be because of ease of access to products containing synthetic cannabinoids and the inability to easily test for synthetic cannabinoids using current clinical tests, parole and probation drug tests, and routinely used military and civilian workplace drug tests.^{4,5,15,16} There are several published reports describing the presentation, treatment, and outcome of ED patients who have ingested synthetic cannabinoids. The patients described in these reports range in age from 13 to 59.^{8,22,23,24} For all of the aforementioned reasons, it has been suggested that clinicians, especially in the ED, be constantly on the alert for synthetic cannabinoid toxicity symptoms, even if drug screen results are negative.⁵

Education about the dangers of synthetic cannabinoids needs to be provided to the general public, the medical community, and retailers.¹⁹ Educators can help prevent use of synthetic cannabinoids by addressing use of these substances in programs designed to prevent illicit drug use, such as the White House Office of National Drug Control Policy's Drug-Free Communities Program.¹⁹ Parents can also discuss the dangers of these drugs with their children and use parental controls for online purchases. Recent survey results show that such interventions may have already resulted in teens being less likely to use "synthetic marijuana" because past year use among 12th graders dropped from 11.3 percent in 2012 to 7.9 percent in 2013.²⁵ However, it is important to note that this same survey indicates that 8th, 10th and 12th graders report a low level of perceived risk of using synthetic cannabinoids once or twice.²⁵ Because most synthetic cannabinoid-related ED visits result in discharge, a patient's time in the ED is a valuable opportunity for intervention and education.

Most importantly, medical professionals need to understand the effects of synthetic cannabinoids, so that supportive care and treatment can be provided to patients who experience their adverse effects. Suggested treatment recommendations include intravenous fluids, administration of benzodiazepine medications, and possibly antipsychotic medication if symptoms are severe.²⁶ With new drugs of abuse, it is difficult to disseminate information about their effects when they have only recently been identified and their effects have not yet been studied in a comprehensive way. Furthermore, the changing composition of products containing synthetic cannabinoids, and the inability of routinely used clinical laboratory tests to detect these substances, makes it difficult for treating physicians to make a clear diagnosis and establish a treatment plan for the intoxicated patient. Health professionals in the ED can seek information from other sources, such as medical toxicologists or poison control center staff, who may be better informed about new designer drugs.²⁷

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SUGGESTED CITATION

Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (October 16, 2014). Update: Drug-Related Emergency Department Visits Involving Synthetic Cannabinoids. Rockville, MD.

SUMMARY

Synthetic cannabinoids are dangerous products which are sold as a legal high and marketed towards youth with names such as “Spice,” and “K2.” Although regulatory agencies have attempted to stop the distribution of these products manufacturers continually change their chemical structures to evade current laws and regulations. In 2012 and 2013, CDC investigated outbreaks that involved synthetic cannabinoids in multiple states. Based on our analysis using data from the Drug Abuse Warning Network (DAWN), the number of visits made to emergency departments (EDs) that involved synthetic cannabinoids more than doubled between 2010 and 2011 (11,406 visits in 2010 to 28,531 visits in 2011). When stratified by age, the rate of ED visits increased more than fourfold for those aged 18 to 20 (from 13.8 visits per 100,000 population in 2010 to 60.8 visits per 100,000 population in 2011) and doubled for those aged 12 to 17 (from 14.9 visits per 100,000 population in 2010 to 30.2 visits per 100,000 population in 2011). In 2011, synthetic cannabinoids were the only substance involved in 65 percent of ED visits by those aged 20 or younger. These results demonstrate the harmful effects of synthetic cannabinoids, especially on youth, and how education continues to be needed for parents, the medical community and to retailers who sell such products.

AUTHOR INFORMATION

KEYWORDS

Short Report, Emergency Department Data, Adolescents as Audience, College Students as Audience, Law Enforcement, Men as Audience, Parents and Caregivers, Prevention Professionals, Women as Audience, Marijuana, Synthetic Marijuana

The Substance Abuse and Mental Health Services Administration (SAMHSA) is the agency within the U.S. Department of Health and Human Services that leads public health efforts to advance the behavioral health of the nation. SAMHSA's mission is to reduce the impact of substance abuse and mental illness on America's communities.

The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related morbidity and mortality. DAWN uses a probability sample of hospitals to produce estimates of drug-related emergency department (ED) visits for the United States and selected metropolitan areas annually. DAWN also produces annual profiles of drug-related deaths reviewed by medical examiners or coroners in selected metropolitan areas and States.

Any ED visit related to recent drug use is included in DAWN. All types of drugs – licit and illicit – are covered. Alcohol involvement is documented for patients of all ages if it occurs with another drug. Alcohol is considered an illicit drug for minors and is documented even if no other drug is involved. The classification of drugs used in DAWN is derived from the Multum Lexicon, copyright 2012 Lexi-Comp, Inc., and/or Cerner Multum, Inc. The Multum Licensing Agreement governing use of the Lexicon can be found at <http://www.samhsa.gov/data/emergency-department-data-dawn>.

DAWN is one of three major surveys conducted by SAMHSA's Center for Behavioral Health Statistics and Quality (CBHSQ). For more information on other CBHSQ surveys, go to <http://www.samhsa.gov/data/>. SAMHSA has contracts with Westat (Rockville, MD) and RTI International (Research Triangle Park, NC) to operate the DAWN system and produce publications.

For publications and additional information about DAWN, go to <http://www.samhsa.gov/data/emergency-department-data-dawn>.



U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Substance Abuse & Mental Health Services Administration
Center for Behavioral Health Statistics and Quality
www.samhsa.gov/data



Drug Fact Sheet

K2 or Spice

Overview

K2 or "Spice" is a mixture of herbs and spices that is typically sprayed with a synthetic compound chemically similar to THC, the psychoactive ingredients in marijuana. The chemical compounds typically include HU-210, HU-211, JWH-018, and JWH-073. K2 is commonly purchased in head shops, tobacco shops, various retail outlets, and over the Internet. It is often marketed as incense or "fake weed." Purchasing over the Internet can be dangerous because it is not usually known where the products come from or what amount of chemical is on the organic material.

Street names

Bilss, Black Mamba, Bombay Blue, Fake Weed, Genie, Spice, Zohai

Looks like

K2 is typically sold in small, silvery plastic bags of dried leaves and marketed as incense that can be smoked. It is said to resemble potpourri.



Methods of abuse

K2 products are usually smoked in joints or pipes, but some users make it into a tea.

Affect on mind

Psychological effects are similar to those of marijuana and include paranoia, panic attacks, and giddiness.

Affect on body

Physiological effects of K2 include increased heart rate and increase of blood pressure. It appears to be stored in the body for long periods of time, and therefore the long-term effects on humans are not fully known.

Drugs causing similar effects

Marijuana

Overdose effects

There have been no reported deaths by overdose.

Legal status in the United States

On Tuesday, March 1, 2011, DEA published a final order in the Federal Register temporarily placing five synthetic cannabinoids into Schedule I of the CSA. The order became effective on March 1, 2011. The substances placed into



Drug Fact Sheet

K2 or Spice – cont'd.

Schedule I are 1-pentyl-3-(1-naphthoyl) indole (JWH-018), 1-butyl-3-(1-naphthoyl) indole (JWH-073), 1-[2-(4-morpholinyl) ethyl]-3-(1-naphthoyl)indole (JWH-200), 5-(1,1-dimethylheptyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol (CP-47,497), and 5-(1,1-dimethyloctyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol (cannabicyclohexanol; CP-47,497 C8 homologue). This action is based on a finding by the Administrator that the placement of these synthetic cannabinoids into Schedule I of the CSA is necessary to avoid an imminent hazard to the public safety. As a result of this order, the full effect of the CSA and its implementing regulations including criminal, civil and administrative penalties, sanctions, and regulatory controls of Schedule I substances will be imposed on the manufacture, distribution, possession, importation, and exportation of these synthetic cannabinoids.

Common places of origin

Manufacturers of this product are not regulated and are often unknown since these products are purchased via the Internet whether wholesale or retail. Several websites that sell the product are based in China. Some products may contain an herb called damiana, which is native to Central America, Mexico, and the Caribbean.



American Association of Poison Control Centers

Synthetic Cannabinoid Data
October 31, 2015

These numbers reflect the closed human exposures to synthetic cannabinoid (THC homologs) reported to poison centers as of October 31, 2015. The numbers may change as cases are closed and additional information is received.

Year	Number of Cases
2011	6,968
2012	5,230
2013	2,668
2014	3,682
2015 Through October 31, 2015	6,949

2015 by Month	Number of Cases
January 2015	358
February 2015	273
March 2015	269
April 2015	1,511
May 2015	1,204
June 2015	654
July 2015	740
August 2015	717
September 2015	627
October 2015	596
November 2015	
December 2015	
Total	6,949

Information continues on next page.

2014 by Month	Number of Cases
January 2014	181
February 2014	167
March 2014	205
April 2014	250
May 2014	312
June 2014	337
July 2014	280
August 2014	442
September 2014	395
October 2014	439
November 2014	357
December 2014	315
Total	3,682

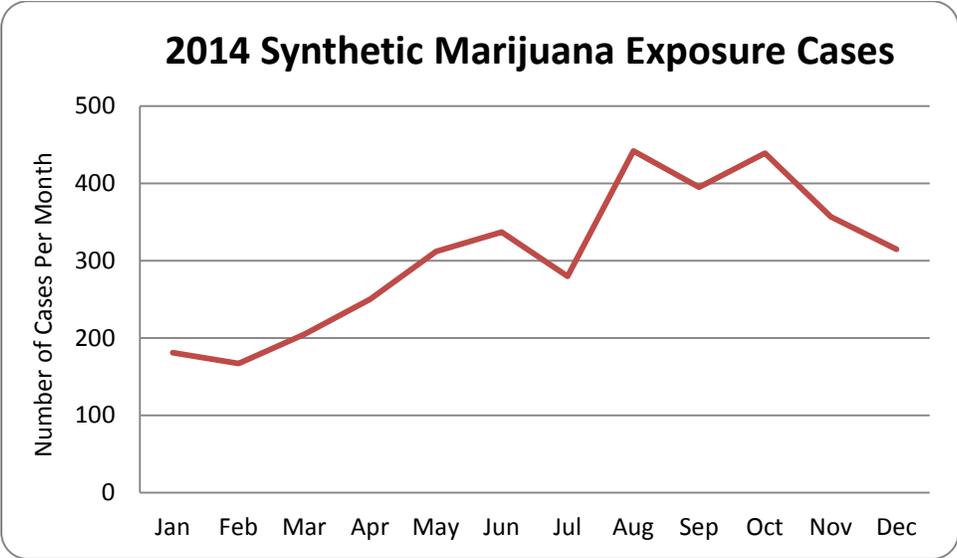
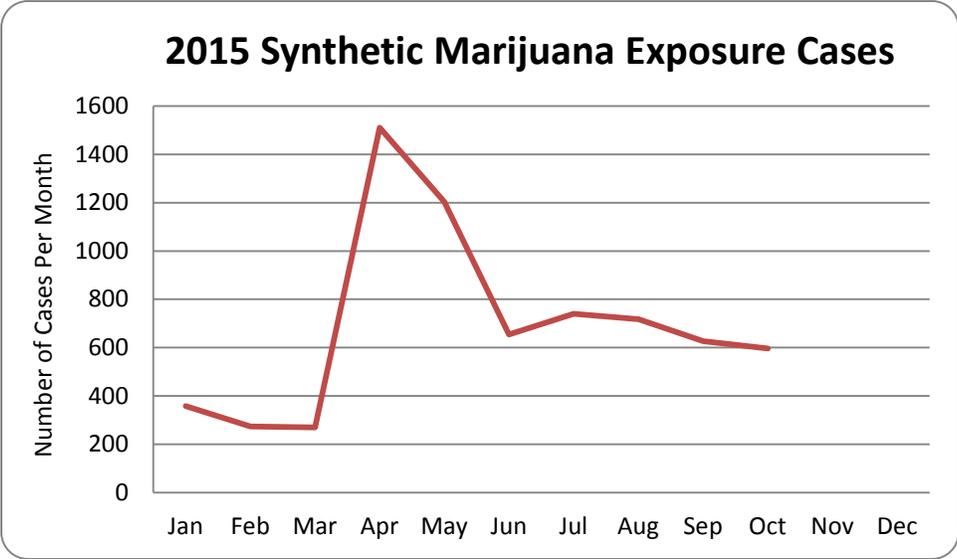
2013 by Month	Number of Cases
January 2013	177
February 2013	252
March 2013	253
April 2013	267
May 2013	277
June 2013	230
July 2013	186
August 2013	204
September 2013	213
October 2013	200
November 2013	209
December 2013	200
Total	2,668

2012 by Month	Number of Cases
January 2012	657
February 2012	634
March 2012	644
April 2012	498
May 2012	507
June 2012	497
July 2012	459
August 2012	346
September 2012	315
October 2012	252
November 2012	202
December 2012	219
Total	5,230

Please note: American Association of Poison Control Center data for this year and last is considered preliminary because it is possible that a poison center may update a case anytime during the year if new information is obtained. In the fall of each year, the data for the previous year is locked, and no additional changes are made.

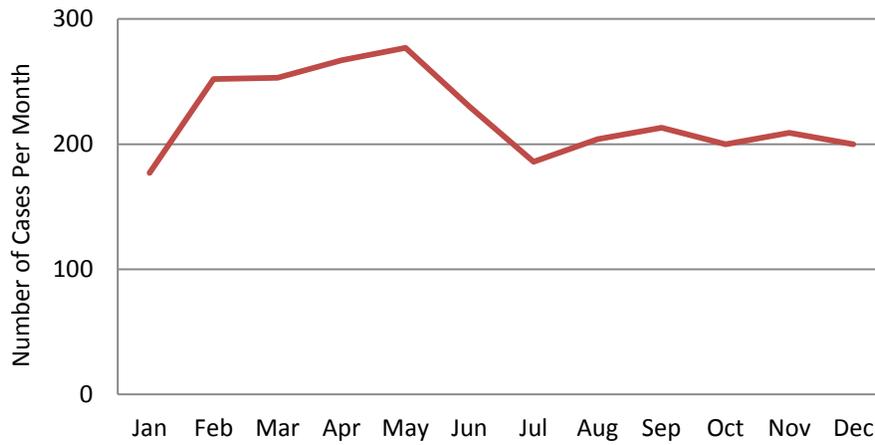
The term “exposure” means someone has had contact with the substance in some way; for example, ingested, inhaled, absorbed by the skin or eyes, etc. Not all exposures are poisonings or overdoses.

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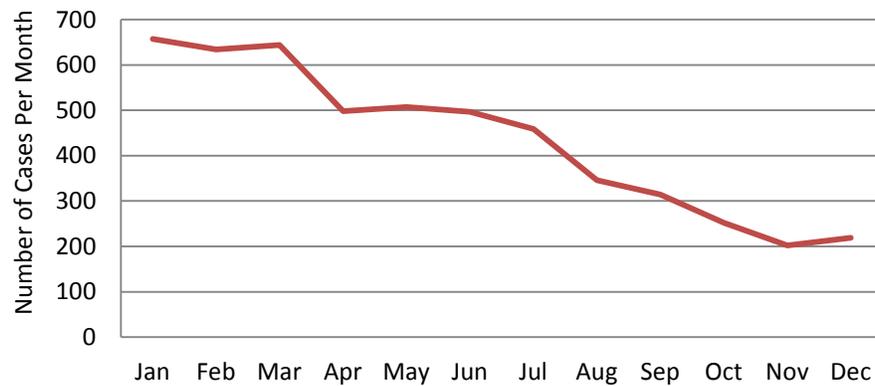


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2013 Synthetic Marijuana Exposure Cases



2012 Synthetic Marijuana Exposure Cases



2011 Synthetic Marijuana Exposure Cases





American Association of Poison Control Centers

Synthetic Cannabinoid Data
November 30, 2015

These numbers reflect the closed human exposures to synthetic cannabinoid (THC homologs) reported to poison centers as of November 30, 2015. The numbers may change as cases are closed and additional information is received.

Year	Number of Cases
2011	6,968
2012	5,230
2013	2,668
2014	3,682
2015 Through November 30, 2015	7,369

2015 by Month	Number of Cases
January 2015	358
February 2015	273
March 2015	269
April 2015	1,511
May 2015	1,204
June 2015	654
July 2015	740
August 2015	717
September 2015	627
October 2015	596
November 2015	420
December 2015	
Total	7,369

Information continues on next page.

2014 by Month	Number of Cases
January 2014	181
February 2014	167
March 2014	205
April 2014	250
May 2014	312
June 2014	337
July 2014	280
August 2014	442
September 2014	395
October 2014	439
November 2014	357
December 2014	315
Total	3,682

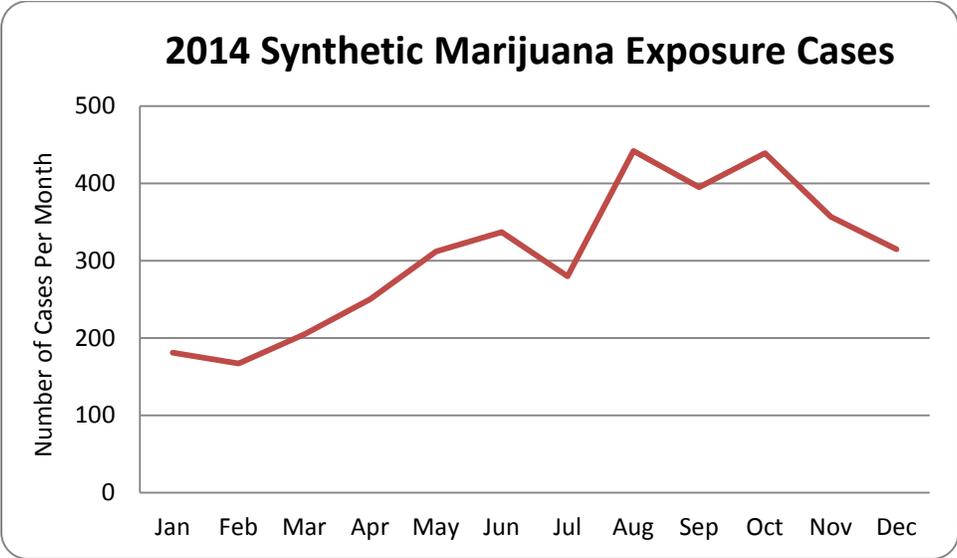
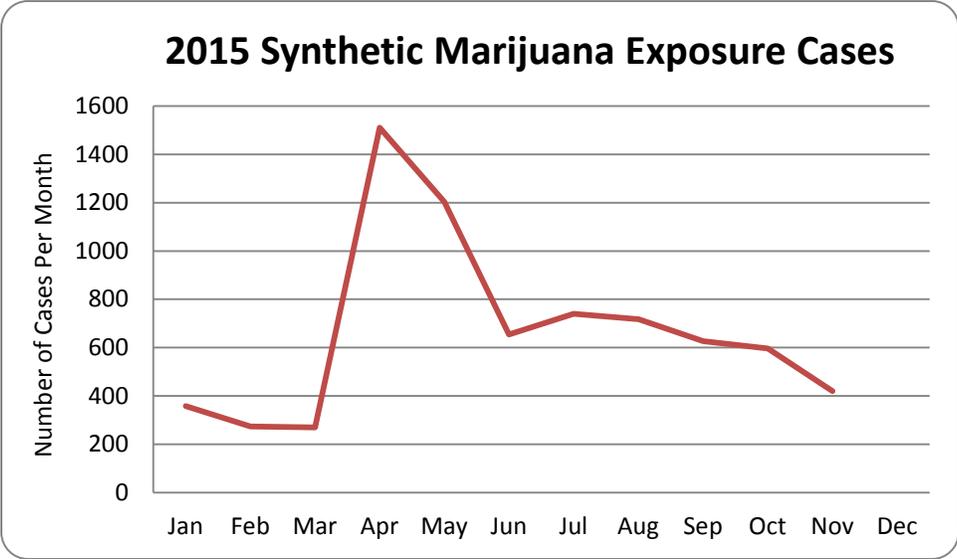
2013 by Month	Number of Cases
January 2013	177
February 2013	252
March 2013	253
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May 2013	277
June 2013	230
July 2013	186
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September 2013	213
October 2013	200
November 2013	209
December 2013	200
Total	2,668

2012 by Month	Number of Cases
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Total	5,230

Please note: American Association of Poison Control Center data for this year and last is considered preliminary because it is possible that a poison center may update a case anytime during the year if new information is obtained. In the fall of each year, the data for the previous year is locked, and no additional changes are made.

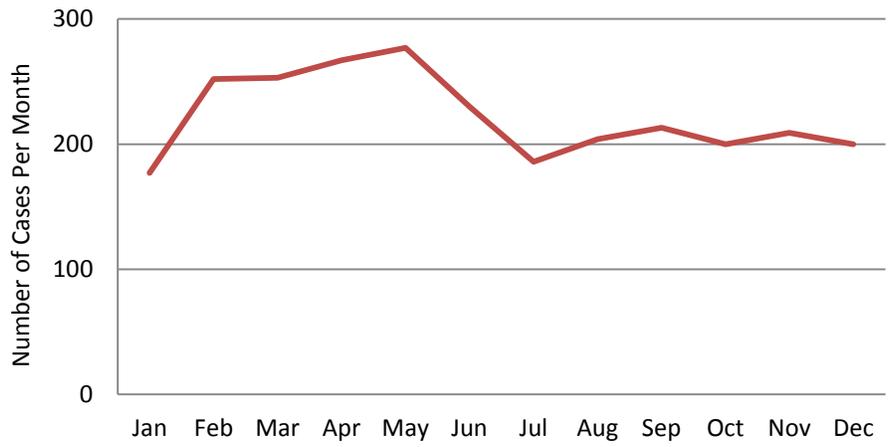
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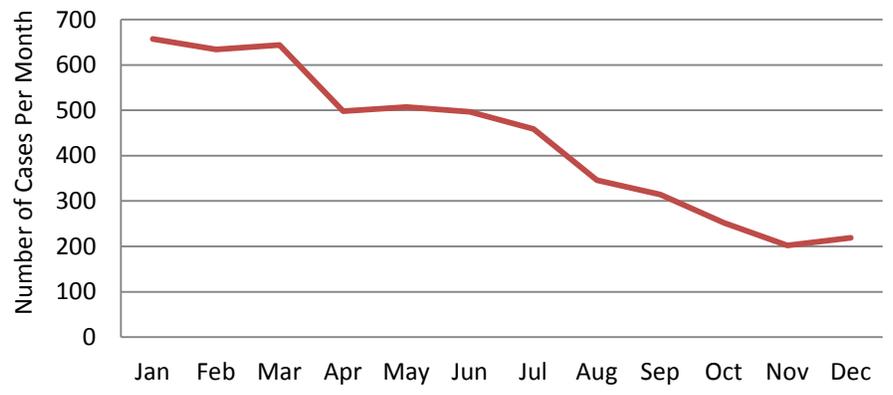


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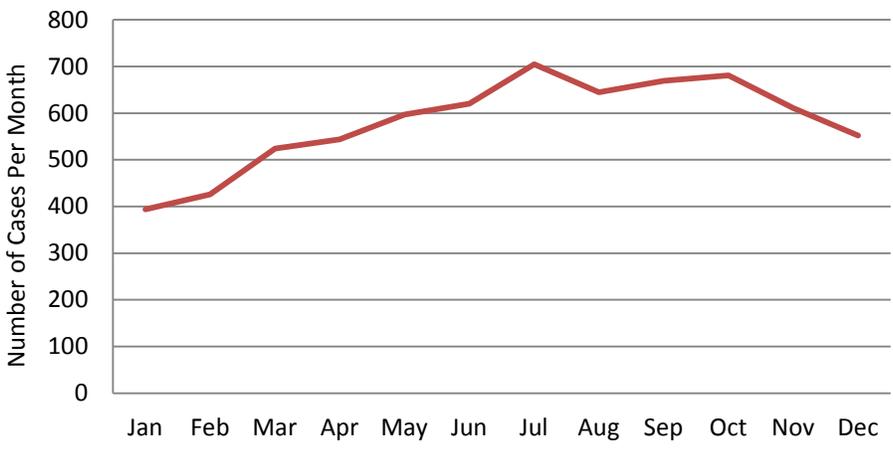
2013 Synthetic Marijuana Exposure Cases



2012 Synthetic Marijuana Exposure Cases



2011 Synthetic Marijuana Exposure Cases



Rise in Synthetic Marijuana Use by Teens an Issue Locally and Nationally

A form of synthetic marijuana, commonly referred to as “Spice” or “K2”, began appearing across the U.S. in 2008, and its popularity grew over the past few years mainly because it could be sold legally and not be detected in urinalysis drug tests. However, its legality has been temporarily suspended after the DEA took emergency action in late 2011 by giving five synthetic cannabinoids Schedule 1 status under the Controlled Substances Act (through August 2012), making it illegal to sell, buy, or possess it. While a urinalysis test was recently developed to detect Spice, the test remains cost prohibitive for many jurisdictions to include in their regular drug testing panel. Unfortunately, Spice remains available, particularly through black market Internet sites, indicating a need for continued education and prevention¹. As awareness about synthetic marijuana broadened across the U.S., the Monitoring the Future survey added questions in 2011 that asked high school seniors about their experience using these drugs, with nearly 1 in 9 (11%) reporting they had used them in the past year (not shown)².

Locally, SANDAG added new questions about Spice to their 2011 Substance Abuse Monitoring (SAM) interview conducted in Juvenile Hall with recently arrested youth. As Table 1 shows, these interviews revealed that one in every two juvenile arrestees had ever tried Spice, with 41 percent having done so in the past year and 18 percent having used it as recently as three days prior to their arrest. The youth who had ever tried Spice did so for the first time on average at age 15.17 ($SD=1.30$, range 11 to 18 years) (not shown).

Table 1

MORE THAN HALF OF LOCAL JUVENILE ARRESTEES EVER TRIED SPICE	
Ever tried Spice	52%
Used Spice in last year	41%
Used Spice in last 3 days	18%
TOTAL	124

NOTE: Cases with missing information not included

SOURCE: Substance Abuse Monitoring Survey, 2011

Through the SAM project, SANDAG will continue to monitor trends in arrestees’ use of Spice to determine if recent federal controls on its availability and developing drug screens have an effect on its use among this population. In June 2012, SANDAG will release its SAM bulletin summarizing 2011 data from interviews with juvenile arrestees. To access the SAM bulletin and other SANDAG publications, go to www.sandag.org/cj. For more information about Spice, visit the National Institute of Drug Abuse Web site at www.drugabuse.gov.

¹ National Institute on Drug Abuse. (2011). InfoFacts: Spice. Available [on-line] at www.drugabuse.gov.

² Johnston, L.D., O’Malley, P., Bachman, J.G., and Schulenberg, J.E. (2011). *Monitoring the Future national results on adolescent drug use: Overview of key findings, 2011*. Ann Arbor: Institute for Social Research, The University of Michigan.

Parents Warn Against Synthetic Marijuana After 19-Year-Old Son Dies

POSTED 11:25 PM, AUGUST 7, 2014, BY KTLA 5 WEB STAFF AND LU PARKER,
UPDATED AT 06:29AM, AUGUST 8, 2014



A California teen recently died after smoking one hit of synthetic marijuana, and now his parents are on a mission to prevent similar deaths from happening. "In a moment of peer pressure, he gave into that, thinking that was OK, it was somehow safe, and one hit later he goes to sleep and never wakes up," Connor Reid Eckhardt's father said. Effects of smoking the often-legal product can include altered mental state, irregular heartbeat and seizures. Watch KTLA's video here: <http://ktlanc.ws/1mt0eLL>

Parents of a 19-year-old California teen who recently died after smoking synthetic marijuana spoke to KTLA about trying to prevent similar deaths from happening in the future.

On July 11, Connor Eckhardt inhaled one hit of dried herbs that had been sprayed with chemicals to cause a pot-like high, his parents said.

“In a moment of peer pressure, he gave into that, thinking that was OK, it was somehow safe, and one hit later, he goes to sleep and never wakes up,” Connor’s father, Devin Eckhardt, said.

Connor Eckhardt quickly slipped into a coma and experienced brain swelling, his parents said.

Effects of smoking the often-legal product include altered mental state, irregular heartbeat and seizures, the [Los Angeles Times](#) reported.

“These substances are not benign,” Dr Andrew Monte, the lead author of an editorial in the New England Journal of Medicine, said. “You can buy designer drugs of abuse at convenience stores and on the Internet. People may not realize how dangerous these drugs can be – up to 1,000 times stronger binding to cannabis receptors when compared to traditional marijuana.”

Since Connor Eckhardt’s death, his parents fulfilled his wish to have his organs donated and [created a Facebook page](#) meant to carry on his memory and tell others about his untimely death.

Reports of Synthetic Cannabinoids Overdoses in the United States

Synthetic Marijuana Suspected in 3 Deaths, 75 Hospitalizations in Colorado (Colorado)

September 9th, 2013

<http://www.drugfree.org/join-together/synthetic-marijuana-suspected-in-3-deaths-75-hospitalizations-in-colorado/>

Almost 120 People In Texas Overdose On Synthetic Marijuana In Just 5 Days; All Linked To Same Dallas-Based Supplier (Texas)

May 7, 2014

<http://www.medicaldaily.com/almost-120-people-texas-overdose-synthetic-marijuana-just-5-days-all-linked-same-dallas-based-280814>

Governor Hassan Declares State of Emergency as a Result of Overdoses from Synthetic Cannabinoid (New Hampshire)

August 14, 2014

<http://governor.nh.gov/media/news/2014/pr-2014-08-14-emergency.htm>

Mississippi and Alabama 'Spice' Overdoses Send More Than 300 to ER in 2 Weeks (Mississippi and Alabama)

Apr 16, 2015

<http://abcnews.go.com/Health/mississippi-alabama-spice-overdoses-send-300-er-weeks/story?id=30362036>

Governor Cuomo Issues Health Alert: Illegal Synthetic Marijuana Sends More Than 160 New Yorkers to the Hospital Since April 8 (New York)

APRIL 17, 2015

<http://www.governor.ny.gov/news/governor-cuomo-issues-health-alert-illegal-synthetic-marijuana-sends-more-160-new-yorkers>

Spice Causes More Than 50 Overdoses In 11 Days (Maryland and Virginia)

April 21, 2015

<http://www.your4state.com/news/news/spice-causes-more-than-50-overdoses-in-11-days>

Spice overdoses now an 'epidemic' for Tucson

July 23, 2015

<http://www.tucsonnewsnow.com/story/29620570/spice-overdose-calls-stressing-city-resources>

Attachment 3

Study of Expanded Use of an Automated Delivery Device

UPDATE 12-14-15

Jan D. Hirsch, BPharm, PhD

UCSD Skaggs School of Pharmacy & Pharmaceutical Sciences



Update

- ScriptCenter Kiosk Installation
 - Location
 - Progress and timeline
- Update on Study
 - Reminder of Research Questions
 - Updated Timeline

ScriptCenter Kiosk Location Sharp Memorial Hospital

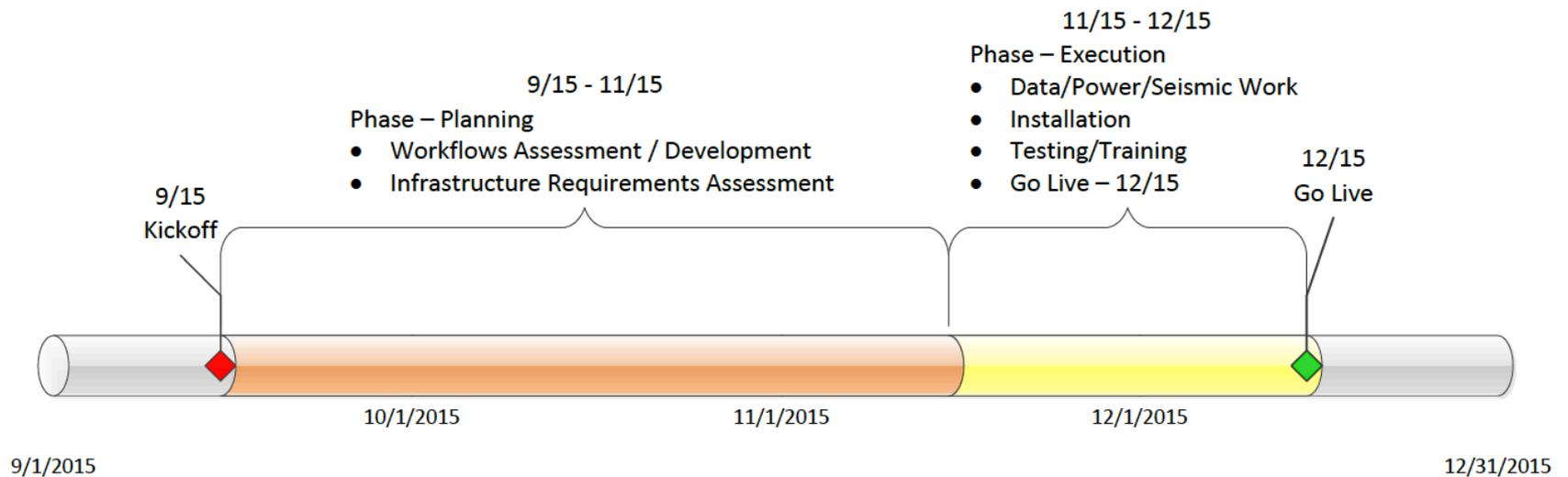


Sharp Memorial Hospital employee entrance located on ground floor. Secure access only.

ScriptCenter Kiosk Installation



Asteres ScriptCenter Implementation, Sharp Memorial Hospital



After 12/15/15 “go-live” date

- Employees will be able to enroll to use the kiosk
- Employees will be encouraged to use the ScriptCenter to feel how it works – before they have enrolled to really use for their prescriptions.
 - There will also be a spokesperson at machine during set times.
- Employees will be able to receive forms from the ScriptCenter to allow them to “transfer” their prescriptions to the SRS Pharmacy for future delivery to the Script Center
- Email will be sent to employees with current prescriptions – for them to be able to transfer their Rx's to the Script Center
- Marketing at the regular pharmacy counter also will be telling people about possibility of transfer – plus other opportunities as the as the marketing plan progresses

Study Research Questions

Primary: Is patient *primary adherence* (prescription retrieval rate; all prescriptions) greater for kiosk vs.

- Historical and concurrent regular counter rate?
- Rx retrieval rate based on Return to Stock (RTS) rate per month

RTS rate = # Rxs RTS after 14 days/# Rxs filled

Secondary: Kiosk vs. Regular Counter Patients

- Is number or nature of questions for pharmacists during consultation for new prescriptions different? (*consultation log*)
- What is mean time from fill (RPh verified) to pick up?

Kiosk patients:

- Satisfaction with access to pharmacist for questions & convenience

Sharp Memorial Hospital employees:

- Would kiosk be beneficial and increase primary adherence?

Study Design

Quasi-experimental with
non-randomized control group

- Pre-Kiosk Implementation Survey (Sharp Employees)

Kiosk Start

6 months pre-kiosk

Month 1

Month 6

Regular Counter

- RTS rate*

Kiosk

- RTS rate
- Consultation Log
- Time to Pick-up
- Kiosk Patient Satisfaction

Regular Counter

- RTS rate*
- Consultation Log (1 week sample pts w/ new Rx)
- Time to Pick-up*

RTS = Return to Stock

* For employees and dependents

Projected Study Timetable

- Q4 2015 Pre-kiosk 6-month data collection phase begins

- Q1 2016 Implement Kiosk device (12/15/15)
Refine data collection tools & process
Deployment of program/enroll patients

- Q2 & Q3 2016 Post-kiosk implementation
Data collection and analysis

- Q4 2016 Report Results to Board



Questions?

UC San Diego
SKAGGS SCHOOL OF PHARMACY
AND PHARMACEUTICAL SCIENCES

Attachment 4

Preventing Diversion in the ED

Philippe Mentler, PharmD, BCPS

Although drug addiction in the general population is well studied and documented, limited epidemiologic surveillance data exist on addiction and drug diversion patterns among health care workers (HCWs). In fact, the dearth of evidence might suggest that drug diversion among HCWs is uncommon or poses no harm, but, unfortunately, the opposite is true. The rates of opiate and benzodiazepine abuse, for example, are higher among HCWs than among the population at large.¹ One possible reason for this is their almost ubiquitous access to, and extensive knowledge of, controlled substances. It is not unusual for HCWs to conflate their understanding of therapeutic and toxic doses, pharmacokinetics, and addictive potential with a false sense of control over these agents.

Drug diversion by HCWs poses significant risks to the diverter, the hospital, and to patients. For example, patients may receive incorrect medications or lower doses than prescribed, resulting in inadequate pain control or sedation. Drug diversion also can confer a significant risk of infection. In one case, 45 patients contracted hepatitis C from a radiology technician who was injecting himself with fentanyl and reusing the syringes during patient procedures.² As a result of this one HCW's diversion, almost 5,000 patients were potentially exposed to, and required testing for, hepatitis C.³

Because of the potential risks, it is important to be able to identify drug diversion and prevent it whenever possible. Although diversion of controlled substances receives the most attention, diversion of non-controlled agents, for example, by the nauseated employee who pockets an ondansetron, or the worker who snatches sildenafil for street sale, is no less important and should be addressed in hospital drug diversion policies.

Detecting Diversion

Identifying drug diversion is challenging, as anyone, regardless of their academic degrees and accomplishments, work ethic, or personality, can become addicted to controlled substances. An impaired HCW often appears normal and may maintain a high level of productivity, particularly in the early stages of addiction. To identify a potential diverter, management must keep an open mind, remove any prejudices, and pay close attention to subtle changes in behavior, such as:

- Taking long breaks or disappearing from the floor for prolonged periods
- Exhibiting mood swings throughout the workday
- Being exceptionally helpful (eg, frequently offering to administer medications, particularly controlled substances, for other nurses)
- Staying beyond a scheduled shift or coming to the workplace on days off
- Being prone to mistakes, such as automated dispensing cabinet (ADC) miscounts, or frequently dropping pills or breaking vials
- Wearing long sleeves to conceal injection drug use

HCWs can divert controlled substances in countless ways. Common methods include retaining wasted product for future use or removing multiple tablets or capsules when only one is ordered for the patient. Despite the risk of needle exposure, diverters also have stolen sharps containers to retrieve discarded drugs (see **TABLE 1**).

Preventing Diversion

A multifaceted approach, including use of technology, policy adherence, staff education, and robust oversight, is necessary to prevent diversion. Most of the technology aimed at drug diversion-prevention pertains to ADCs. For example, individually locking bins have been available since ADCs were introduced into hospitals. More recently, diversion-detection software has become available, which allows a hospital to record typical usage and waste patterns for specific areas or ADCs in the hospital. These data then can be used as benchmarks for individual staff and groups of employees, to highlight and flag aberrance in practice patterns.

For example, imagine two ED ADCs have a combined typical usage of 100 units per day of hydromorphone 1 mg. Sixty percent typically comes from ADC 1, and 40% from ADC 2. The average nurse pulls 10 units per day, with a standard deviation (SD) of 2. Nurse Bob's average pull is 12 units per day. Over a short period, the ADC software report shows an increase in Bob's withdrawals per day to 18 units (SD >3). In addition, he has changed where he pulls hydromorphone; although he formerly used ADC 1 exclusively, he now alternates between the two machines. As a result, the report is flagged, and a review is initiated.

It should be noted that while available software helps in preventing diversion, facilities should maintain a human component when monitoring ADCs and avoid relying solely on software reports. Hospitals also should limit access to ADCs; HCWs should use only the ADC at their primary workstation. In addition, facilities should update access to ADCs regularly as personnel move to different primary work areas. Passwords should be changed at least every 6 months, and personnel must be trained to never share their passwords. Wasting must be witnessed, and should occur at the time the drug is removed from the ADC.

Diversion awareness is important for all hospital employees. Education should be included in all employee orientations and continued, at a minimum, as part of the institution's annual competencies. The curriculum should include the risks of addiction, common diversion behaviors, the process for reporting suspicious behaviors, and a review of the hospital's controlled substances policy.

Implementing a Diversion Response Team

Developing a formalized drug diversion response team is recommended for the prevention and detection of drug diversion and the enforcement of drug diversion policies. A diversion response team should be multidisciplinary in nature, including representation from pharmacy, nursing, medical staff, security, and human resources. A response team with dedicated FTEs is necessary to interpret data, review suspected cases, conduct interviews, and document outcomes. A dedicated team also allows team members to develop greater expertise in diversion methods, which leads to more professional, confidential, and expedited diversion investigations and a more robust enforcement program. A valuable resource for institutions considering the implementation of a drug diversion response team is available from the Minnesota State Department (<http://www.health.state.mn.us/patientsafety/drugdiversion/divroadmap041812.pdf>).

Helping the Addicted HCW

Some health care systems are reluctant to report diversion or offer drug addiction support for fear of negative publicity, added scrutiny by regulatory agencies, or employee retaliation. However, HCW drug addiction is a treatable disorder with a high treatment success rate. Studies show that the abstinence rates of various groups of chemically dependent HCWs who receive treatment for addiction exceed 80%, which is significantly greater than that of the general population.⁴

TABLE 4 Methods Used to Divert and to Prevent Diversion	
Common Methods Used to Divert Controlled Substances	Methods to Prevent Diversion*
Saving excess product that should have been wasted	<ul style="list-style-type: none"> Implement a policy that another staff member must witness waste at the time of ADC withdrawal
Preceding to drop product on the floor or breaking a vial and wasting it in the ADC	<ul style="list-style-type: none"> Require physical return to pharmacy with a report of all products that are considered contaminated
Removing product after a patient has left the hospital	<ul style="list-style-type: none"> Enforce rapid discharge and inscription of patient from the ADC upon discharge Use ADC diversion-prevention software
Spicing off a portion of the contents of a product and replacing with saline	<ul style="list-style-type: none"> Take patient complaints of limited pain relief seriously Product should never be left unattended The HCW responsible for the patient should both remove and administer product
Using a co-worker's ADC password to obtain product or act as second waste witness	<ul style="list-style-type: none"> Implement a policy of not sharing passwords Require password changes at least every 6 months Use ADC diversion-prevention software
Switching a similar looking product for a controlled substance prior to administration	<ul style="list-style-type: none"> Review look-alike products in ADCs Run regular reports and investigate discrepancies of non-controlled substances Use ADC diversion-prevention software
Removing remnants of disposed product from sharps bins	<ul style="list-style-type: none"> Use specialized waste bins that contain controlled substances or render them otherwise unusable
Removing more product than was ordered	<ul style="list-style-type: none"> Have a policy whereby only the amount of product needed at the lowest dosage strength is removed for each valid order Use ADC diversion-prevention software
"Forgetting" product in a shirt pocket and requesting waste on the following day	<ul style="list-style-type: none"> Require product be sent to pharmacy for testing and a report be completed for the event Consider drug testing HCWs in this scenario
Removing product for a crashed good patient from a separate unit	<ul style="list-style-type: none"> Limit ADC access only to those working on a given unit Maintain and regularly update user access of ADCs Use ADC diversion-prevention software
Removing product by override and asking for a physician order afterward	<ul style="list-style-type: none"> Prohibit the practice or create specific circumstances for which a controlled substance override is allowed (i.e. high level trauma, rapid sequence intubation, seizure) Use ADC diversion-prevention software

Conclusion

Although the dearth of evidence might suggest the opposite, controlled substance addiction and drug diversion actually are quite common among HCWs. As any employee can divert drugs, it is the responsibility of all hospital employees to be aware of drug diversion practices and immediately report suspicious behavior. A number of tools are available to aid in the detection of drug diversion, but tools are successful only when humans remain engaged in the process and use them correctly. Once diversion with the intent to use is proven, it is imperative that the institution offers the diverter entry into a treatment program for the benefit of the diverter and for the safety of the public at large.

References

1. Baldisseri MR. Impaired healthcare professional. *Crit Care Med*. 2007;35(suppl 2):S106-S116.
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4. Cross W, Bologeorges S, Angres D. Issues and Data Associated with Addictive Disease in Pharmacists. *US Pharm*. November, 2013. http://www.uspharmacist.com/continuing_education/ceviewtest/lessonid/109516/. Accessed July 7, 2015.



Philippe Mentler, PharmD, BCPS, is a senior medication management consultant with VHA, Inc. He joined VHA after more than 10 years as an emergency department pharmacist.

Philippe received his doctorate of pharmacy from Ernest Mario School of Pharmacy, and completed a PGY1 general practice residency at the University of Illinois at Chicago and a PGY2 residency in emergency medicine at Robert Wood Johnson University Hospital in conjunction with the Ernest Mario School of Pharmacy.

CASE STUDY 1

The Moody Veteran Nurse

A skilled and trusted ED nurse with more than 20 years of experience was caught diverting injectable opiates. He admitted to diversion and to his addiction only after another nurse witnessed multiple wasted medications in his pocket. His addiction to pain medications began after a simple surgical procedure the prior year. When his physician limited his pain medications, he began diverting from the hospital. The nurse had been taking on extra assignments and completing other nurses' tasks in order to increase access to opiates, and he wore long sleeves to hide track marks from multiple daily injections. In retrospect, staff members noted that he tended to have mood swings during the workday.

CASE STUDY 2

Medication Substitution

A nurse asked the emergency pharmacist to speak with an irate patient, a regular at the hospital and a known drug seeker. The patient complained that the generic 512s (a street name for oxycodone/acetaminophen, derived from the fact that the number 512 is imprinted on the branded 5 mg Percocet tablet) prescribed do not work. This was the third time in a week that the patient was in the ED complaining of not receiving pain relief from the hospital's 512s. The following day, a pharmacy technician reported to the ED pharmacist that he had to replace a large number of missing prednisone 50 mg tablets for the second time within a week. Upon initiating an investigation, the ADC report on prednisone showed that one nurse performed a cancelled transaction every time a discrepancy was noted (several more prednisone discrepancies were identified during the investigation). When the nurse was confronted, she admitted filling the oxycodone/acetaminophen orders with prednisone tablets prior to patient administration. She removed the tablet from its unit-dose container and placed it in a unit-dose cup prior to entering the patient's room. Prednisone 50 mg is almost identical in size and appearance to 5 mg oxycodone/acetaminophen.



Prednisone 50 mg

Oxycodone/
acetaminophen 5/325 mg

CASE STUDY 3

Mishandling Confirmed Diversion

A pharmacist with a history of brief employment in numerous pharmacy settings was hired to staff the evening shift of the central pharmacy. Within 3 months, discrepancies in the controlled substances cabinet were noted. One evening, a pharmacy technician witnessed the pharmacist pocket several oxycodone tablets. The technician reported the incident directly to pharmacy administration. The pharmacist was immediately offered the choice to resign, which she eagerly accepted. She then went on to work in a retail pharmacy where she was caught on video stealing a handful of hydrocodone/acetaminophen from a 1000-count bottle. She was again offered the option to resign from that position, and accepted. The actions of both of these facilities—which are intended to serve and care for the public—place the general population at continued risk and leaves adrift a person with a treatable disease. Instead, the addict should have been offered access to an addiction treatment program, and the offenses should have been reported to the appropriate authorities.

Attachment 5

SETTLEMENT AGREEMENT

This Settlement Agreement (“Agreement”) is made and entered into by and between the United States of America, acting through the United States Department of Justice and its Drug Enforcement Administration (“DEA”) (collectively, the “United States”), and The General Hospital Corporation, d/b/a Massachusetts General Hospital, and its sole member, The Massachusetts General Hospital (collectively, “MGH”) (together, the “Parties”).

Recitals

- A. MGH is the largest hospital in Massachusetts, the largest teaching hospital of Harvard Medical School, and a biomedical research facility. It currently holds twelve active DEA registrations as set forth in Attachment 1 hereto.
- B. Each DEA registrant is required to conduct its operations in accordance with the Controlled Substances Act, 21 U.S.C. § 801, *et seq.* (the “Act”), and the regulations promulgated thereunder.
- C. The DEA is the Department of Justice component agency primarily responsible for enforcing the Act and is vested with the responsibility of investigating violations of the Act.
- D. The United States Attorney General, through the United States Attorney’s Office, has primary authority to bring civil actions to enforce the Act. See 21 U.S.C. § 871 and 28 C.F.R. § 0.55(c).
- E. The United States contends that, during the period from October 4, 2011, through April 1, 2015, MGH negligently failed to make, keep, or furnish certain records required to be kept under the Act, and failed to provide effective controls and procedures to guard against theft and loss of controlled substances. More specifically, the United States contends that it has civil

claims against MGH for engaging in the alleged conduct described in the United States'

Statement of Relevant Conduct set forth in Attachment 2 and as follows:

1. MGH failed to notify the DEA of nurse J.S.'s theft of controlled substances within one business day of discovery, in violation of 21 C.F.R. § 1301.76(b);
2. MGH failed to notify the DEA of nurse J.Z.'s theft of controlled substances within one business day of discovery, in violation of 21 C.F.R. § 1301.76(b);
3. MGH failed to provide effective controls and procedures to guard against theft and diversion of controlled substances, in violation of 21 C.F.R. § 1301.71;
4. MGH failed to maintain complete and accurate records of all controlled substances that it received, sold, delivered, or otherwise disposed of, in violation of 21 C.F.R. §§ 1304.21 and 1304.22(c);
5. MGH failed to document 358 transfers of Schedule II controlled substances using the required DEA Form 222, in violation of 21 C.F.R. § 1305.03;
6. MGH failed to document 407 transfers of Schedule IV controlled substances with invoices, in violation of 21 C.F.R. § 1304.22(b);
7. The MGH medical practice with DEA registration number xxxxxx349 failed to conduct an initial inventory, in violation of 21 C.F.R. § 1304.11(b);
8. The MGH medical practice with DEA registration number xxxxxx349 and the MGH pharmacy with DEA registration number xxxxxx423 failed to conduct biennial inventories, in violation of 21 C.F.R. § 1304.11(c);
9. MGH's inpatient pharmacy conducted a biennial inventory that was incomplete, in violation of 21 C.F.R. § 1304.11(a) and (c); and

10. MGH failed to maintain current and accurate records of controlled substances in its automatic drug-dispensing machines (“ADMs”), in violation of 21 C.F.R. § 1304.22(a).

The conduct referred to in this Recital E and Attachment 2 is referred to below as the Covered Conduct.

In consideration of the mutual promises and obligations of this Agreement, the Parties agree and covenant as follows:

Terms of Agreement

1. No later than 10 days after the date on which this Agreement is signed by all Parties, MGH shall pay the United States Two Million, Three Hundred Thousand Dollars (\$2,300,000.00) (the “Settlement Amount”). The Settlement Amount shall be paid by electronic funds transfer pursuant to written instructions from the United States.

2. No later than 10 days after the date on which this Agreement is signed by all Parties, MGH and DEA will enter into the three-year Corrective Action Plan (“CAP”) that is Attachment 3 hereto.

3. In consideration of the obligations of MGH in this Agreement, conditioned upon MGH’s timely paying the Settlement Amount and entering into the CAP, and subject to the conditions in Paragraph 4, the United States releases MGH and Partners Healthcare System, Inc. (“Partners”), and their assigns, successors, principals, management, officers, directors, agents, and employees, from any civil or administrative claims the United States has, could have, or may assert in the future related to the Covered Conduct under the Act.

4. This Agreement in no way alters or restricts the United States’ right to enforce the Act and regulations promulgated thereunder by commencing a civil or administrative action

against MGH or Partners for any violations of the Act which are not based on the Covered Conduct, nor does it restrict the United States or any other sovereign or governmental entity from bringing any criminal charge against MGH, Partners, or any employee of either MGH or Partners. Also, this Agreement does not prevent any sovereign other than the United States from pursuing civil, criminal, and/or administrative claims against MGH or Partners for the Covered Conduct and/or any other conduct. However, this Agreement in no way waives MGH's or Partners' right to raise any defenses in any such actions.

5. MGH and Partners release the United States and its agencies, officers, agents, employees, and servants, from any claims (including for attorney's fees, costs, and expenses of every kind and however denominated) that MGH and/or Partners has asserted, could have asserted, or may assert in the future against the United States or its agencies, officers, agents, employees, or servants, related to the Covered Conduct and the United States' investigation and prosecution thereof.

6. The obligations imposed upon MGH pursuant to this Agreement and the CAP are in addition to, and not in derogation of, all requirements imposed upon MGH pursuant to all applicable federal, state, and local laws and regulations, including but not limited to the requirements set forth in Title 21 of the United States Code and the regulations promulgated thereunder.

7. Each party and signatory to this Agreement represents that it/he/she freely and voluntarily enters into this Agreement without any degree of duress or compulsion.

8. This Agreement is intended to be for the benefit of the Parties only; it does not create any rights or benefits as to third parties. The Parties do not release any claims against any other person or entity.

9. This Agreement is governed by the laws of the United States. The exclusive jurisdiction and venue for any dispute relating to this Agreement is the United States District Court for the District of Massachusetts. This Agreement shall be deemed to have been drafted by all Parties to this Agreement and shall not, therefore, be construed against any Party for that reason in any subsequent dispute.

10. This Agreement and the CAP constitute the complete agreement between the Parties. This Agreement may be amended only by a writing signed by all Parties.

11. The undersigned counsel represent and warrant that they are fully authorized to execute this Agreement on behalf of the Parties.

12. This Agreement may be executed in counterparts, each of which constitutes an original and all of which constitute one and the same agreement.

13. This Agreement is binding on MGH's successors, transferees, and assigns.

14. Nothing in this Agreement constitutes an agreement by the United States concerning the characterization of the Settlement Amount for purposes of the Internal Revenue laws, Title 26 of the United States Code.

15. Each Party shall bear its own legal and other costs incurred in connection with this matter, including the preparation and performance of this Agreement.

16. All parties consent to the United States' disclosure of this Agreement, and information about this Agreement, to the public, except that the names and contact information in paragraph 3 of Attachment 3 may be redacted and kept confidential.

17. The Parties may execute this Agreement via facsimile and/or by portable document format (.pdf), both of which shall be deemed the equivalent of an original signature.

18. This Agreement shall be effective on the date of signature of the last signatory to the Agreement ("Effective Date").

THE UNITED STATES OF AMERICA

DATED: 9/28/15

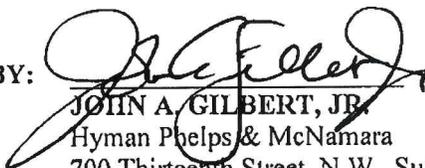
BY: 
JESSICA P. DRISCOLL
Assistant U.S. Attorney
United States Attorney's Office
District of Massachusetts

MASSACHUSETTS GENERAL HOSPITAL

DATED: 9/28/15

BY: 
TOBY R. UNGER
Partners HealthCare System
50 Staniford Street, 10th Floor
Boston, MA 02114

DATED: 9/28/15

BY: 
JOHN A. GILBERT, JR.
Hyman Phelps & McNamara
700 Thirteenth Street, N.W., Suite 1200
Washington, D.C. 20005

Attachment 1: MGH's Active DEA Registrations

DEA #	Address	City	Reg. Type
xxxxxxx433	55 Fruit Street	Boston	Hospital/Clinic
xxxxxxx926	55 Fruit Street	Boston	Hospital/Clinic
xxxxxxx423	55 Fruit Street	Boston	Research
xxxxxxx349	165 Cambridge Street	Boston	Hospital/Clinic
xxxxxxx242	32 Fruit Street	Boston	Analytical Lab
xxxxxxx293	73 High Street	Charlestown	Hospital/Clinic
xxxxxxx569	133 ORNAC	Concord	Hospital/Clinic
xxxxxxx755	40 Second Avenue	Waltham	Hospital/Clinic
xxxxxxx355	300 Ocean Avenue	Revere	Hospital/Clinic
xxxxxxx664	151 Everett Avenue	Chelsea	Hospital/Clinic
xxxxxxx288	102 Endicott Street	Danvers	Hospital/Clinic
xxxxxxx933	52 Second Avenue	Waltham	Hospital/Clinic

Attachment 2: United States' Statement of Relevant Conduct

The United States alleges that the following occurred during the period October 4, 2011, through April 1, 2015.

1. DEA began its investigation after learning that MGH nurse J.S. had stolen 14,492 pills from an automated drug-dispensing machine (“ADM”), and MGH nurse J.Z.1 had stolen 1,429 pills from a different ADM. Most of the pills they stole were oxycodone, a Schedule II drug. MGH did not discover J.S.’s actions until she had been stealing for an entire year – even though she sometimes appeared high to co-workers and other times was seen falling asleep at work. MGH failed to report these diversions to DEA within one business day as required by 21 C.F.R. § 1301.76(b).

2. In November-December 2013, DEA investigators conducted accountability audits of sample controlled substances in MGH’s inpatient pharmacy and its outpatient pharmacy. The government alleges that the audits revealed 16,681 missing or extra pills at the inpatient pharmacy, and 7,177 missing or extra pills at the outpatient pharmacy. Most of the missing or extra pills were oxycodone, a Schedule II controlled substance.

3. The government alleges that MGH failed to provide effective controls and procedures to guard against theft and diversion of controlled substances, in violation of 21 C.F.R. § 1301.71. Many of these deficiencies concerned ADMs which MGH kept in locked medication rooms, operating rooms (“ORs”), and pharmacies. For example:

- a. During the period October 9, 2013, through December 31, 2013, MGH relied on a pharmacy information system (“PIS”) to generate inventory figures for its ADMs in response to a request by DEA. However, the PIS data did not match the ADM data.
- b. During the period October 4, 2011, through May 2014, patient names remained active in the ADMs up to 72 hours post-discharge. This was one way that J.S. and J.Z.1 were able to divert drugs.
- c. On November 5, 2013, MGH documents listed one doctor, S.J., as having access to ADMs even though S.J. had left MGH four months earlier.
- d. On November 5, 2013, MGH documents listed another doctor, T.A., as having access to the ADMs even though T.A. had surrendered his medical license and his DEA registration in early 2013.
- e. Sometimes ADMs had inaccurate readings of dosage units. For example, during a DEA audit on October 31, 2013, one ADM showed that it contained 22 lorazepam 0.5 mg pills. However, DEA investigators found not only the 22 lorazepam 0.5 mg pills, but also another cartridge in the machine containing an additional 25 lorazepam pills that was not registering on the machine’s computer.

- f. From October 4, 2011, through May 2014, MGH staff could access drugs in some ADMs for up to two minutes before lockout occurred. This extended time period before lockout allowed users to continue to access the machine and make multiple withdrawals.
- g. From October 4, 2011, through February 2014, the inpatient pharmacy staff were not alerted to medication overrides in ADMs. (A medication override occurs when a staff member enters his/her user ID and password into an ADM to get medication for a patient; the ADM displays a list of all patients in the unit and their medication orders; and the staff member selects either a higher dose than what is listed for the patient or a medication not on that patient's list.) Both nurses referenced in paragraph 1 above diverted drugs by using medication overrides.

4. The government alleges that certain members of MGH management demonstrated a supervisory failure to provide effective controls and procedures to guard against theft and diversion of controlled substances, in violation of 21 C.F.R. § 1301.71. For example:

- a. From October 4, 2011, through March 2014, many nursing supervisors failed to regularly review ADM reports to look for possible diversion, and some, including J.Z.1's supervisor, were not aware how often they were expected to review the reports. Failure to regularly review ADM reports enabled diversion by allowing medication overrides and "wrong bin opened" incidents to go undetected.
- b. When asked why MGH waited so long to implement controlled substance surveillance software, which produces user-friendly reports of ADM data indicating potential drug diversion, one MGH manager told the DEA that MGH is "rooted in tradition" and "change doesn't happen fast around here."
- c. MGH uses an anesthesia electronic health record ("EHR") to document the amounts of controlled substances administered in each OR. On occasions when the anesthesia EHR for a particular surgery did not match the drug kit reconciliation for that surgery, the OR pharmacy asked the medical personnel involved to address the discrepancy.
- d. A certified registered nurse anesthetist, A.S., lost small amounts of controlled substances three different times within eight months. She was not disciplined.
- e. Another certified registered nurse anesthetist, S.W., lost controlled substances four different times within eight months. She was not disciplined. S.W.'s supervisor told the DEA that she chose to have only an "offhand conversation" with S.W. about these incidents because S.W. was up for a promotion and she did not want to hurt S.W.'s chances.

5. The government alleges that MGH also failed to provide effective controls and procedures to guard against theft and diversion of controlled substances, in violation of 21 C.F.R. § 1301.71, as follows:

- a. From October 4, 2011, until December 2013, every OR at MGH contained an unlocked “Bluebell” cart in which medical staff stored their controlled substances when on break.
- b. During the period October 4, 2011, until November 1, 2012, some anesthesia residents who needed controlled substances for 9:30 am cases signed them out early and took them to off-campus grand rounds at 7:00 am. MGH did not discipline residents for this practice.
- c. On November 14, 2011, three syringes of hydromorphone, remifentanyl, and morphine were found in various ORs. No one knew where they came from or to whom they belonged.
- d. In November 2011, an MGH inpatient pharmacy manager reported 20 syringes of morphine were missing from the pharmacy vault during unit moves and renovations.
- e. An MGH physician, E.P., repeatedly prescribed controlled substances for patients without seeing them and without maintaining medical records, in 2012-2013. His patients included at least one who was simultaneously obtaining prescriptions for controlled substances from other physicians. E.P. voluntarily surrendered his DEA registration in 2014.
- f. From October 4, 2011, through December 2013, medical personnel often took controlled substances with them to lunch at the on-site hospital cafeteria as a matter of convenience.

6. The government alleges that, as a result of MGH’s failure to provide effective controls and procedures to guard against theft and diversion of controlled substances, in violation of 21 C.F.R. § 1301.71, theft and diversion occurred, and not just by J.S. and J.Z.1. For example:

- a. In May 2014, MGH discovered that nurse M.B. had been diverting controlled substances (oxycodone, Percocet, Dilaudid, Valium, Ativan, morphine, Flexeril, and Vicodin) from the emergency room for four years. MGH was unable to determine the amount she diverted.
- b. In May 2014, MGH discovered that nurse M.M. had diverted Dilaudid for seven years (2007-2010 and 2012-2014).
- c. In June 2014, MGH discovered 34 drug transaction discrepancies that nurse J.L. was unable to explain. The drugs at issue were Ativan, Dilaudid, fentanyl, ketamine, Valium, morphine, and Versed. The nurse denied

diverting the drugs and blamed the discrepancies on lack of documentation and the rushed pace in the emergency room.

- d. In August 2014, MGH discovered that R.C., a pediatric surgery nurse, had had a substance abuse issue off and on for the past twelve years. He was found sleeping at work, unsteady on his feet, and with slurred speech. He admitted diverting Dilaudid, a Schedule II drug, and injecting himself at work.
- e. In August 2014, MGH discovered that nurse J.Z.2 had repeatedly taken home controlled substances, allegedly by mistake, and provided no documentation of waste. (All controlled substances signed out must be used, returned, or wasted. In all cases, the amounts must be documented.)
- f. In December 2014, 42 vials of controlled substances were found in the apartment of a deceased MGH anesthesia resident, who was determined to have died of natural causes. Five of the vials contained MGH labels.
- g. In January 2015, nurse C.F. admitted to diverting various quantities of narcotic waste, including fentanyl, Versed and Demerol, at least 25 times in the past year.

7. The government acknowledges that, since the start of the DEA's diversion investigation in October 2013, MGH has taken significant steps to improve its controls and procedures against theft and diversion of controlled substances, including adoption of the Corrective Action Plan set forth in Attachment 3.

Attachment 3 - Corrective Action Plan

This Corrective Action Plan (“CAP”) between Massachusetts General Hospital (“MGH”) and the U.S. Drug Enforcement Administration (“DEA”) memorializes the policies and procedures that MGH and the DEA (jointly, the “Parties”) have agreed upon to advance MGH’s efforts to ensure compliance with the Controlled Substances Act (the “Act”) and to enhance MGH’s ability to prevent, detect, and address drug diversion.

1. This CAP is incorporated by reference at paragraph 2 of the Settlement Agreement between MGH and the United States dated September 28, 2015 (the “Settlement Agreement”).

2. The period of this CAP shall be three years, starting on the Effective Date of the Settlement Agreement.

3. Whenever this CAP requires notice to the DEA, the persons to be notified will be [REDACTED] and [REDACTED]

[REDACTED]. Whenever this CAP requires notice to MGH, the person to be notified will be [REDACTED]. Either party may change the name and/or contact information of its contact person(s) by so notifying the other party’s contact person(s).

4. MGH represents that it began to implement certain diversion controls (“Enhanced Controls”) following the commencement of the DEA’s diversion investigation in October 2013. MGH agrees to promptly complete implementation of the Enhanced Controls at all twelve of its current DEA registrations (as identified on Attachment 1 to the Settlement Agreement), and at every facility that receives a DEA registration during the term of this CAP. The Enhanced Controls include the following:

- a. Employing a full-time Drug Diversion Compliance Officer.
- b. Establishing a drug diversion team consisting of the Drug Diversion Compliance Officer; members of the compliance, pharmacy, and nursing departments; and MGH Police & Security. The drug diversion team is tasked with preventing, monitoring, and responding to incidents of drug diversion.
- c. Conducting mandatory annual training for all staff with authorized access to controlled substances, including training on the signs and symptoms of substance abuse and addiction, drug diversion monitoring and prevention, the duty to report, and the filing of safety reports.
- d. Purchasing controlled substance surveillance software, which produces user-friendly reports of automatic drug-dispensing machine (“ADM”) data indicating potential drug diversion.
- e. Replacing Bluebell carts in all MGH main campus operating rooms with ADMs; having a timed password-reset for all ADMs (every 90 days); and implementing a biometric identification system (fingerprints) on all ADMs .
- f. Permitting only pharmacists and directly supervised nationally certified pharmacy technicians to have access to the pharmacy vault.
- g. Permitting only authorized MGH pharmacy or IT employees to have access to the ADM server.
- h. Requiring the MGH Department of Pharmacy to conduct daily reviews of ADM reports, including but not limited to instances where more than a certain number of pills were dispensed at one time for one patient (“greater than”

reports), destock verifications, null transactions, medication overrides, and discrepancies.

- i. Requiring the MGH Department of Pharmacy to conduct daily operating room post-case reconciliation (“PCR”) of controlled substances dispensed, used, or wasted, and, if any discrepancy is not resolved within 72 hours, to report the discrepancy to the Drug Diversion Compliance Officer.
- j. Requiring at least one nursing leader per clinical area: (i) to conduct weekly reviews of all controlled substance surveillance software anomalous usage reports for the ADMs in that clinical area; and (ii) to conduct daily reviews (Monday through Friday) of controlled substance surveillance software reports of controlled substances dispensed from the ADMs in that clinical area.
- k. Requiring clinical nursing supervisors to review “greater than” ADM reports on Saturdays, Sundays, and holidays.
- l. Requiring Associate Chief Nurses to conduct monthly compliance checks on their nursing leader direct reports.
- m. Requiring trend and pattern reports to be reviewed quarterly by the Drug Diversion Team.

5. MGH will take the following corrective actions in addition to the Enhanced

Controls:

- a. MGH will hire external auditors to conduct unannounced audits at all MGH facilities with active DEA registrations (including all pharmacies and ADMs)

of five Schedule II-V controlled substances randomly chosen by the auditors.

The audits will be conducted at:

- i. 100% of MGH's DEA-registered facilities during the first 12 months following the effective date of this CAP;
- ii. 50% of MGH's DEA-registered facilities between months 13 and 24;
and
- iii. 25% of MGH's DEA-registered facilities between months 25 and 36.

Each audit report will be reviewed and signed by the Pharmacist in Charge or the registrant's DEA-designated person. MGH will have 30 days to cure any deficiencies or resolve any discrepancies, and its efforts to cure will be documented in the audit report. If the auditors find any material discrepancies or other material issues (*e.g.*, diversion, missing records, significant losses), MGH will send the audit report to DEA within five business days after the end of the 30-day cure period. MGH will maintain the audit records, and make them available for review by the DEA upon request, for two years after this CAP expires.

- b. During each year of this CAP, MGH will conduct a self-evaluation of all of its DEA-registered facilities to review compliance with all requirements of the Act, the regulations issued under the Act, and this CAP. At the completion of each evaluation, the Pharmacist in Charge or the DEA-designated person at the registrant will certify that he/she has completed the evaluation and document any corrective action to be taken. MGH will retain the letters of

certification, and make them available to the DEA upon request, for two years following the expiration of this CAP.

- c. MGH will maintain all ADM data for two years after the data is created. MGH will maintain the data in a readily retrievable manner and produce it to the DEA upon request.
- d. MGH will maintain reports of disciplinary action taken against employees found to have lost a significant quantity of controlled substances, or found to have stolen or otherwise diverted controlled substances. To the extent authorized by state or federal privacy laws and regulations, MGH will maintain the reports in an easily accessible manner and produce them to the DEA upon request.
- e. MGH will create and enforce a written policy of progressive discipline applicable to all employees with access to controlled substances.
- f. MGH will promptly investigate all thefts, significant losses, and other potential diversion of controlled substances. MGH will promptly report all such thefts, significant losses, and other diversions to DEA. DEA is aware that MGH has additional reporting duties to licensure boards, and all other relevant agencies (*e.g.*, the Drug Control Program of the Massachusetts Department of Public Health).
- g. If MGH makes a report to an agency that any of its employees has lost or stolen controlled substances, MGH will promptly send a copy of the report to the DEA. If MGH makes a report to an agency that any of its employees has abused or mishandled controlled substances (without a report of loss or theft),

MGH will promptly notify DEA that a report has been made, including the name of the agency and the date of the report.

- h. MGH will promptly notify the DEA when a member of the Drug Diversion team, as identified above in paragraph 4(b), becomes aware that any MGH employee has been arrested or charged by law enforcement on any charges related to theft or diversion of controlled substances.

6. MGH will complete biennial inventories of all of its DEA-registered facilities using physical counts (including counts of all ADMs), witnessed by two individuals.

7. MGH will comply at all times with the Act and the regulations issued thereunder. To the extent that any requirements in the Act or regulations are greater than those imposed by this CAP, the stricter requirements will apply.

8. Each Party and signatory to this CAP represents that it/he/she freely and voluntarily enters into this CAP without any degree of duress or compulsion.

9. This CAP is intended for the benefit of the Parties only; it does not create any rights or benefits for third parties.

10. This CAP is governed by the laws of the United States. The exclusive jurisdiction and venue for any dispute relating to this CAP is the United States District Court for the District of Massachusetts. This CAP shall be deemed to have been drafted by both Parties and shall not, therefore, be construed against either Party in any subsequent dispute.

11. This CAP and the Settlement Agreement constitute the complete agreement between the DEA and MGH relating to the matters addressed herein. This CAP may be amended only by a writing signed by both DEA and MGH.

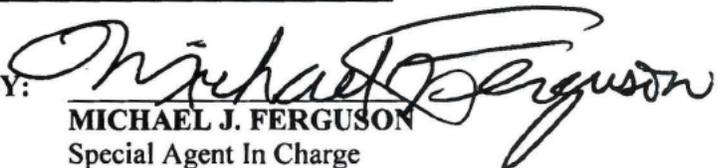
12. The undersigned signatories represent and warrant that they are fully authorized to execute this CAP on behalf of the parties.

13. This CAP may be executed in two counterparts, each of which constitutes an original and both of which constitute one and the same agreement.

14. This CAP is binding on MGH's successors, transferees, and assigns.

THE U.S. DRUG ENFORCEMENT ADMINISTRATION

DATED: 9/28/15

BY: 

MICHAEL J. FERGUSON
Special Agent In Charge
New England Field Division
15 New Sudbury St., Room E-400
Boston, MA 02203


NANCY COFFEY
Program Manager, Diversion
15 New Sudbury St., Room E-400
Boston, MA 02203

MASSACHUSETTS GENERAL HOSPITAL

DATED: _____

BY: _____

TOBY R. UNGER
Partners HealthCare System
50 Staniford Street, 10th Floor
Boston, MA 02114

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DATED: 9/28/15

BY:



TOBY R. UNGER
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50 Staniford Street, 10th Floor
Boston, MA 02114

Attachment 6

1707.2 Duty to Consult.

- (a) A pharmacist shall provide oral consultation to his or her patient or the patient's agent in all care settings:
 - (1) upon request; or
 - (2) whenever the pharmacist deems it warranted in the exercise of his or her professional judgment.
- (b) (1) In addition to the obligation to consult set forth in subsection (a), a pharmacist shall provide oral consultation to his or her patient or the patient's agent in any care setting in which the patient or agent is present:
 - (A) whenever the prescription drug has not previously been dispensed to a patient; or
 - (B) whenever a prescription drug not previously dispensed to a patient in the same dosage form, strength or with the same written directions, is dispensed by the pharmacy.
- (2) When the patient or agent is not present (including but not limited to a prescription drug that was shipped by mail) a pharmacy shall ensure that the patient receives written notice: of his or her right to request consultation; and a telephone number from which the patient may obtain oral consultation from a pharmacist who has ready access to the patient's record.
- (3) A pharmacist is not required by this subsection to provide oral consultation to an inpatient of a health care facility licensed pursuant to section 1250 of the Health and Safety Code, or to an inmate of an adult correctional facility or a juvenile detention facility, except upon the patient's discharge. A pharmacist is not obligated to consult about discharge medications if a health facility licensed pursuant to subdivision (a) or (b) of Health and Safety Code Section 1250 has implemented a written policy about discharge medications which meets the requirements of Business and Professions Code Section 4074.
- (c) When oral consultation is provided, it shall include at least the following:
 - (1) directions for use and storage and the importance of compliance with directions; and
 - (2) precautions and relevant warnings, including common severe side or adverse effects or interactions that may be encountered.
- (d) Whenever a pharmacist deems it warranted in the exercise of his or her professional judgment, oral consultation shall also include:
 - (1) the name and description of the medication;
 - (2) the route of administration, dosage form, dosage, and duration of drug therapy
 - (3) any special directions for use and storage;
 - (4) precautions for preparation and administration by the patient, including techniques for self-monitoring drug therapy;
 - (5) prescription refill information;
 - (6) therapeutic contraindications, avoidance of common severe side or adverse effects or known interactions, including serious potential interactions with known nonprescription medications and therapeutic contraindications and the action required if such side or adverse effects or interactions or therapeutic contraindications are present or occur;
 - (7) action to be taken in the event of a missed dose.
- (e) Notwithstanding the requirements set forth in subsection (a) and (b), a pharmacist is not required to provide oral consultation when a patient or the patient's agent refuses such consultation.

Attachment 7

In the event that the board is not able to convene a public meeting on regular notice or pursuant to the emergency meeting provisions of the Open Meetings Act, any three members of the board may convene a meeting by teleconference, by electronic communication (e.g., e-mail), or by other means of communication to exercise the powers delegated to full board pursuant to Business and Professions Code section 4062.

Excerpt from October 2009 Board Meeting

Proposed Delegation to the Board President to Act Pursuant to California Business and Professions Code Section 4062 to Waive Statutory Requirements to Benefit Public Safety in Response to a Declared Emergency or Disaster

Mr. Weisser provided that during the October 2006 Board Meeting, the board voted to adopt a policy statement for pharmacies when providing emergency response. He indicated that a copy of this policy statement was published in the January 2007 issue of *The Script*.

Mr. Weisser provided that Business and Professions Code section 4062 provides the board with broad waiver authority and was recently amended in SB 819 (Chapter 308, Statutes of 2009) to allow for the use of a mobile pharmacy in the event of a declared emergency as specified. He stated that the board intends to use this authority when warranted.

Board Discussion

Ms. Schieldge reviewed the board's options with respect to delegating authority collectively to the board or to an individual board member to waive statutory requirements to benefit public safety in response to a declared emergency or disaster. She recommended that the board limit this authority to situations wherein the board is unable to convene.

The board sought general clarification regarding its options and adherence to the Open Meetings Act. The board reached a consensus to allow any three members of the board to teleconference in the event that the board is unable to convene during a declared emergency. Discussion continued with regards to both the authority of the board and of the Governor during a declared emergency.

Public Comment

President Schell sought clarification regarding what would be achieved during the emergency meeting.

Mr. Room provided that the members attending the emergency meeting would establish and issue guidelines regarding the laws that will be waived during the emergency. There was no additional board discussion or public comment.

4062. Furnishing Dangerous Drugs during Emergency; Mobile Pharmacy

(a) Notwithstanding Section 4059 or any other provision of law, a pharmacist may, in good faith, furnish a dangerous drug or dangerous device in reasonable quantities without a prescription during a federal, state, or local emergency, to further the health and safety of the public. A record containing the date, name, and address of the person to whom the drug or device is furnished, and the name, strength, and quantity of the drug or device furnished shall be maintained. The pharmacist shall communicate this information to the patient's attending physician as soon as possible. Notwithstanding Section 4060 or any other provision of law, a person may possess a dangerous drug or dangerous device furnished without prescription pursuant to this section.

(b) During a declared federal, state, or local emergency, the board may waive application of any provisions of this chapter or the regulations adopted pursuant to it if, in the board's opinion, the waiver will aid in the protection of public health or the provision of patient care.

(c) During a declared federal, state, or local emergency, the board shall allow for the employment of a mobile pharmacy in impacted areas in order to ensure the continuity of patient care, if all of the following conditions are met:

(1) The mobile pharmacy shares common ownership with at least one currently licensed pharmacy in good standing.

(2) The mobile pharmacy retains records of dispensing, as required by subdivision (a).

(3) A licensed pharmacist is on the premises and the mobile pharmacy is under the control and management of a pharmacist while the drugs are being dispensed.

(4) Reasonable security measures are taken to safeguard the drug supply maintained in the mobile pharmacy.

(5) The mobile pharmacy is located within the declared emergency area or affected areas.

(6) The mobile pharmacy ceases the provision of services within 48 hours following the termination of the declared emergency.

Attachment 8

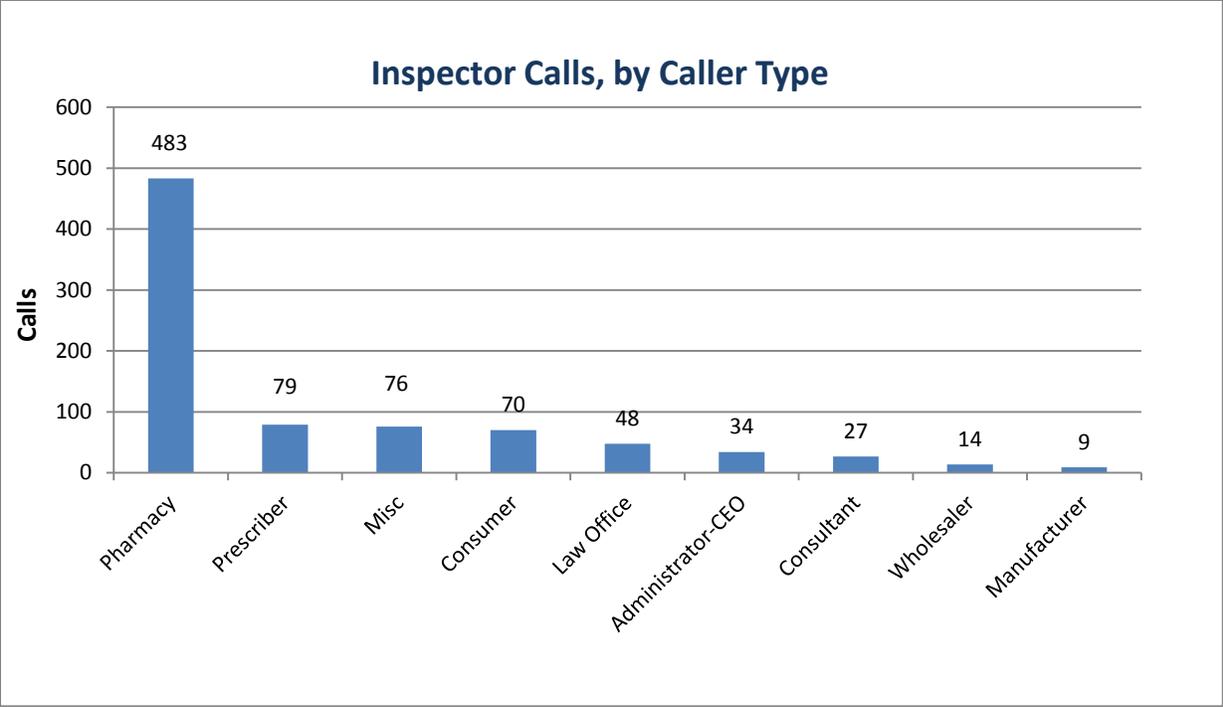
Since July 01, 2015, Pharmacy Board inspectors have responded to 840 calls, an average of 168 calls each month. Our highest month was September, with 252 calls. July was our lowest month, with 100 calls.

Our typical caller is a pharmacist. About half of our callers are pharmacists, and the rest is everyone else. Of the 840 calls inspectors took during this period, 483 callers were pharmacy personnel (406 callers are active pharmacists, or 48 percent of all callers). Some of the other caller groups are: prescribers, consumers, and administrators. However, no single one of these other caller groups stands out. These ratios are stable from each month; pharmacists are consistently the largest single group contacting Board inspectors.

Table: All Inspector Calls

Caller Type	July	August	September	October	November	Total Calls	% of Calls
Administrator-CEO	5	3	17	4	5	34	4%
Consultant	2	6	5	11	3	27	3%
Consumer	9	11	23	12	15	70	8%
Law Office	3	11	14	14	6	48	6%
Manufacturer	1	2	2	2	2	9	1%
Misc.	8	10	22	30	6	76	9%
Pharmacy	56	58	147	125	97	483	58%
Prescriber	14	12	21	16	16	79	9%
Wholesaler	2	7	1	1	3	14	2%
Total	100	120	252	215	153	840	100%
% Growth	na	20%	110%	-15%	-29%		

Chart: All Inspector Calls, by Type of Caller

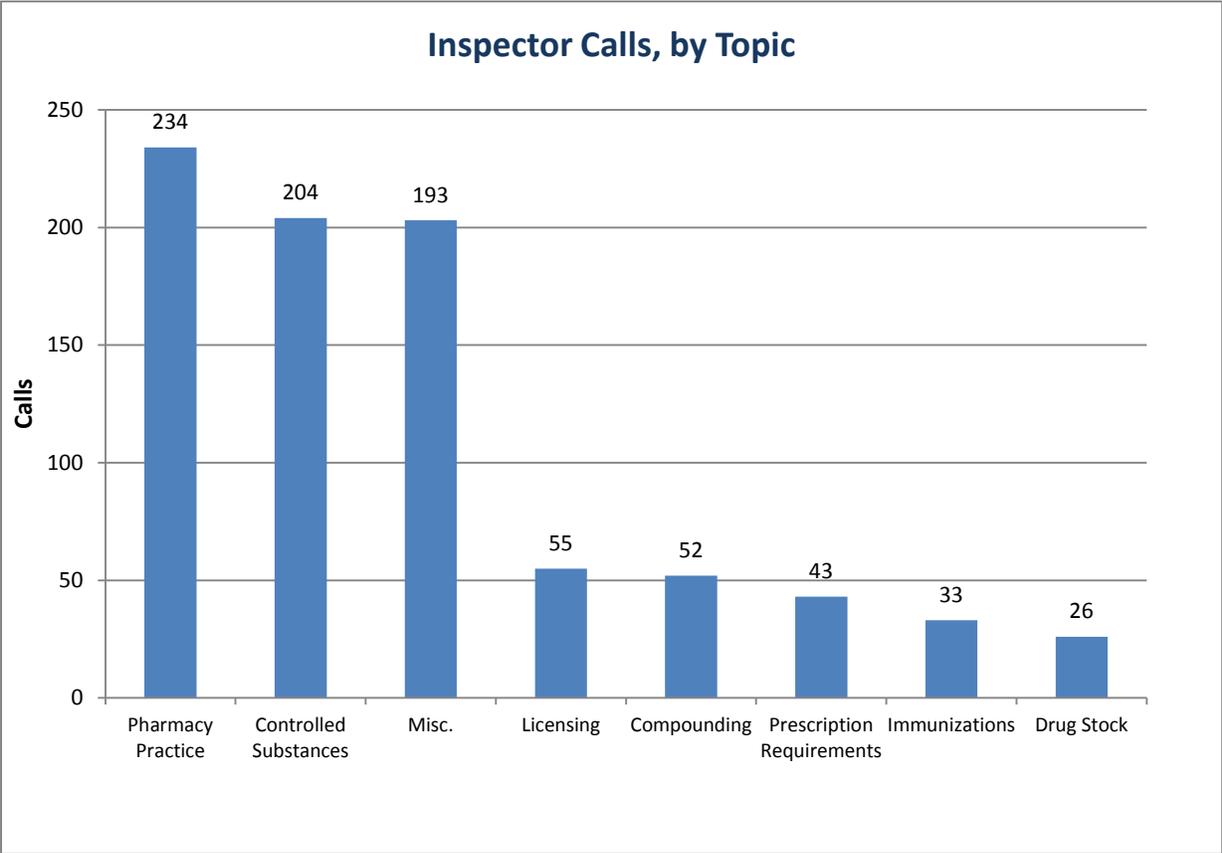


What questions are the inspectors answering? The majority of calls and emails to inspectors are questions regarding general questions about pharmacy practices and regulations regarding controlled substances. However, inspectors answer a wide diversity of questions. About 48 percent of all calls were not directly related to pharmacy practices or controlled substances.

Table: Number of Inspector Calls, by Topic Discussed

Call Topic	No. of Calls	% of Calls
Pharmacy Practice	234	28%
Controlled Substances	204	24%
Misc.	193	23%
Licensing	55	6%
Compounding	52	6%
Prescription Requirements	43	5%
Immunizations	33	4%
Drug Stock	26	3%
Total	840	100%

Chart: All Inspector Calls, by Topic Discussed



Attachment 9

Board of Pharmacy Enforcement Statistics Fiscal Year 2015/2016

Workload Statistics July-Sept Oct-Dec Jan-Mar Apr-June Total 15/16

Complaints/Investigations

Received	730	809			1539
Closed	751	658			1409
4301 letters	12	11			23
Pending (at the end of quarter)	2105	2269			2269

Cases Assigned & Pending (by Team) at end of quarter*

Compliance / Routine Team	787	945			945
Drug Diversion/Fraud	361	460			460
RX Abuse	95	158			158
Compounding	85	74			74
Probation/PRP	51	66			66
Mediation/Enforcement **	325	179			179
Criminal Conviction	401	367			367

Application Investigations

Received	165	149			314
Closed					
Approved	118	94			212
Denied	32	17			49
Total ***	218	149			367
Pending (at the end of quarter)	138	125			125

Letter of Admonishment (LOA) / Citation & Fine

LOAs Issued	56	54			110
Citations Issued	550	453			1003
Total Fines Collected ****	\$451,827.69	\$620,758.49			\$1,072,586.18

* This figure includes reports submitted to the supervisor and cases with SI awaiting assignment.

** This figure include reports submitted to the citation and fine unit, AG referral, as well as cases assigned to enf. Staff

*** This figure includes withdrawn applications.

****Fines collected (through 12/31/2015 and reports in previous fiscal year.)

Board of Pharmacy Enforcement Statistics Fiscal Year 2015/2016

Workload Statistics July-Sept Oct-Dec Jan-Mar Apr-June Total 15/16

Administrative Cases (by effective date of decision)

Referred to AG's Office*	126	101			227
Accusations Filed	73	65			138
Statement of Issues Filed	17	14			31
Petitions to Revoke Filed	2	1			3
Pending					
Pre-accusation	271	269			269
Post Accusation	260	271			271
Total*	600	587			587

Closed

Revocation					
Pharmacist	3	7			10
Intern Pharmacist	1	0			1
Pharmacy Technician	24	26			50
Designated Representative	1	0			1
Wholesaler	0	0			0
Sterile Compounding	0	0			0
Pharmacy	1	2			3

Revocation, stayed; suspension/probation

Pharmacist	4	2			6
Intern Pharmacist	0	0			0
Pharmacy Technician	1	0			1
Designated Representative	0	0			0
Wholesaler	0	0			0
Sterile Compounding	0	0			0
Pharmacy	0	0			0

Revocation, stayed; probation

Pharmacist	11	6			17
Intern Pharmacist	0	0			0
Pharmacy Technician	3	3			6
Designated Representative	0	0			0
Wholesaler	0	0			0
Sterile Compounding	0	1			1
Pharmacy	5	4			9

Surrender/Voluntary Surrender

Pharmacist	3	7			10
Intern Pharmacist	0	0			0
Pharmacy Technician	4	9			13
Designated Representative	0	0			0
Wholesaler	0	0			0
Sterile Compounding	0	0			0
Pharmacy	5	3			8

Board of Pharmacy Enforcement Statistics Fiscal Year 2015/2016

Workload Statistics July-Sept Oct-Dec Jan-Mar Apr-June Total 15/16

Public Reprival/Reprimand

Pharmacist	3	2			5
Intern Pharmacist	0	0			0
Pharmacy Technician	0	0			0
Designated Representative	0	0			0
Wholesaler	0	0			0
Sterile Compounding	1	0			1
Pharmacy	1	1			2

Licenses Granted

Pharmacist	0	0			0
Intern Pharmacist	0	0			0
Pharmacy Technician	3	0			3
Designated Representative	0	0			0
Wholesaler	0	0			0
Sterile Compounding	0	0			0
Pharmacy	0	0			0

Licenses Denied

Pharmacist	0	0			0
Intern Pharmacist	0	0			0
Pharmacy Technician	2	4			6
Designated Representative	0	0			0
Wholesaler	0	0			0
Sterile Compounding	0	0			0
Pharmacy	0	0			0

Cost Recovery Requested**	\$355,106.58	\$308,117.75			\$663,224.33
Cost Recovery Collected**	\$314,805.00	\$85,183.45			\$399,988.45

* This figure includes Citation Appeals

** This figure includes administrative penalties

Immediate Public Protection Sanctions

Interim Suspension Order	3	1			4
Automatic Suspension / Based on Conviction	1	0			1
Penal Code 23 Restriction	8	6			14
Cease & Desist - Sterile Compounding	1	0			1

Board of Pharmacy Enforcement Statistics Fiscal Year 2015/2016

Workload Statistics **July-Sept** **Oct-Dec** **Jan-Mar** **Apr-June** **Total 15/16**

Probation Statistics

Licenses on Probation

Pharmacist	149	151			151
Intern Pharmacist	3	3			3
Pharmacy Technician	37	36			36
Designated Representative	3	3			3
Pharmacy	42	43			43
Sterile Compounding	6	9			9
Wholesaler	2	2			2
Probation Office Conferences	35	27			27
Probation Site Inspections	106	139			139
Successful Completion	5	6			6
Probationers Referred to AG for non-compliance	0	0			0

As part of probation monitoring, the board requires licensees to appear before the supervising inspector at probation office conferences.

These conferences are used as 1) an orientation to probation and the specific requirements of probation at the onset,

2) to address areas of non-compliance when other efforts such as letters have failed, and 3) when a licensee is scheduled to end probation.

As of December 31, 2015.

SB 1441 – Program Statistics

Licensees with substance abuse problems who are either on board probation and/or participating in the Pharmacist Recovery Program (PRP)

Board of Pharmacy	July -Sep	Oct – Dec	Jan-Mar	Apr-Jun	Total 15/16
PRP Intakes					
PRP Self-Referrals	1	1			2
PRP Board Referrals	1	2			3
PRP Under Investigation	3	1			4
PRP In Lieu Of					
Total Number of PRP Intakes	5	4			9
New Probationers					
Pharmacists	3	4			7
Interns		1			1
Technicians	3	2			5
Total New Probationers	6	7			13
PRP Participants and Contracts					
Total PRP Participants	66	63			N/A
Contracts Reviewed	61	60			121
Probationers and Inspections					
Total Probationers	82	85			N/A
Inspections Completed	106	139			245
PRP Referrals to Treatment					
Referrals to Treatment	6	5			11
Drug Tests					
Drug Test Ordered	1006	874			1880
Drug Tests Conducted	974	857			1831
Relapse					
Relapsed	3	7			10
Major Violation Actions					
Cease Practice/Suspension	8	9			17
Termination - PRP	1	1			2
Referral for Discipline		1			1
Exit from PRP or Probation					
Successful Completion	5	3			8
Termination - Probation		1			1
Voluntary Surrender	4				4
Surrender as a result of PTR		1			1
Public Risk	1	1			2
Non-compliance	8	14			22
Other	4	1			5
Patients Harmed					
Number of Patients Harmed	None	None	None	None	None

SB 1441 – Program Statistics

Licensees with substance abuse problems who are either on board probation and/or participating in the Pharmacist Recovery Program (PRP)

Board of Pharmacy	July -Sep	Oct – Dec	Jan-Mar	Apr-Jun	Total 15/16
Drug of Choice at PRP Intake or Probation					
Pharmacists	July-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Total 15/16
Alcohol	2	2			4
Ambien		1			1
Opiates		1			1
Hydrocodone					
Oxycodone					
Morphine					
Benzodiazepines					
Barbiturates					
Marijuana					
Heroin					
Cocaine					
Methamphetamine					
Pharmaceutical Amphetamine					
Phentermine					
Methadone					
Zolpidem Tartrate					
Hydromorphone					
Clonazepam					
Tramadol					
Carisprodol					
Phendimetrazine					
Promethazine w/Codeine					
Intern Pharmacists	July-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Total 15/16
Alcohol		1			1
Opiates					
Hydrocodone					
Oxycodone					
Benzodiazepines					
Barbiturates					
Marijuana					
Heroin					
Cocaine					
Methamphetamine					
Pharmaceutical Amphetamine					
Phentermine					
Methadone					
Zolpidem Tartrate					
Hydromorphone					
Clonazepam					
Tramadol					
Carisprodol					
Phendimetrazine					
Promethazine w/Codeine					
Pharmacy Technicians	July-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Total 15/16
Alcohol	3	1			4
Opiates					
Hydrocodone					
Oxycodone					
Benzodiazepines					
Barbiturates					
Marijuana	1	1			2
Heroin					
Cocaine					
Methamphetamine					
Pharmaceutical Amphetamine		1			1
Phentermine					
Methadone					
Zolpidem Tartrate					
Hydromorphone					
Clonazepam					
Tramadol					
Carisprodol					
Phendimetrazine					
Promethazine w/Codeine					

Drug Of Choice - Data entered from July 2014 to June 2015

- 1 Alcohol
- 2 Opiates
- 3 Hydrocodone
- 4 Oxycodone
- 5 Benzodiazepines
- 6 Barbiturates
- 7 Marijuana
- 8 Heroin
- 9 Cocaine
- 10 Methamphetamine
- 11 Pharmaceutical Amphetamine



Attachment 10

 **FDA Regulatory Actions Involving Drug Compounding**

1

 **Potential Actions**

- Recommend Voluntary Recalls
- Warning Letters
- State Referral Letters
- Injunctions

2

 **Some Factors to Consider**

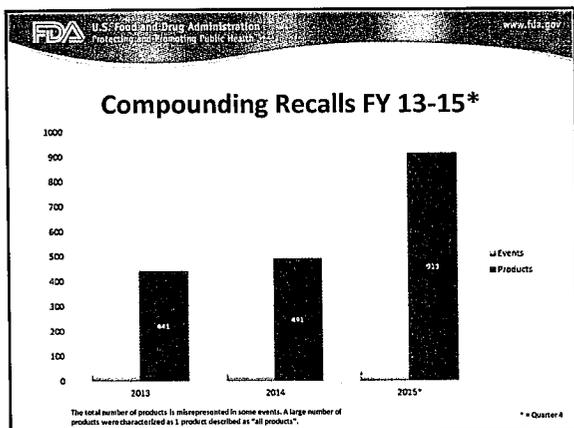
- Risk to public health
 - Lack of sterility assurance
 - Actual contamination
- Prior violations and likelihood of firm compliance
- How easily can the violations be corrected
- Firm's willingness to take voluntary action

3

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Voluntary Actions

- Recalls
 - Since October 2012 there have been over 100 recall events involving compounded drugs, many due to conditions and practices resulting in a lack of drug sterility assurance
 - Some recalls overseen by FDA, others overseen by the state
 - FY 2013 – 30 recall events
 - FY 2014 – 29 recall events
 - FY 2015 – 41 recall events
 - Since October 2012 FDA has issued 3 letters formally asking firms to recall compounded drugs after they refused informal requests



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Voluntary Actions: Examples

- In May 2015, Montana Compounding Pharmacy and Wellness Center ceased operations and recalled all sterile products within expiry after FDA investigators identified, during a surveillance inspection, deviations including: the use of non-sterile drinking water dispensed from a top-loaded bottled water dispenser for use in making injectable drug products; the use of non-sterile, non-pharmaceutical grade ingredients in making injectable drug products; and dog beds, dog fences, and dog hairs within the facility, including in close proximity to the compounding room.
- In September 2015, Medislat (an outsourcing facility) ceased sterile operations and recalled all sterile products within expiry after an FDA inspection of the facility revealed a lack of sterility assurance. FDA had received several reports of adverse events potentially associated with drug products compounded by the firm.

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 **Voluntary Actions**

- Four outsourcing facilities have recalled compounded products
- Recall events by outsourcing facilities are included on FDA's list of outsourcing facilities

<http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm378645.htm>

7

 **Warning Letters**

- Advisory actions – provide notice
- Communicate the Agency's position
- Issued to achieve voluntary and prompt corrective action
- Generally used when there is no history of repeat violations

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 **Warning Letters**

- FDA has issued over 60 warning letters since October 2012
- Many of the warning letters describe violations associated with insanitary conditions

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Warning Letters

Warning letters to facilities not registered as outsourcing facilities under section 503B may also include other violations of the Federal Food, Drug, and Cosmetic Act, and if the firm does not compound in accordance with the conditions of section 503A, these may include violations of requirements for new drug approval, labeling with adequate directions for use, and current good manufacturing practice

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Warning Letters

- Warning letters to facilities registered as outsourcing facilities under section 503B may also include:
 - Violations of current good manufacturing practice (CGMP) requirements (independent of 503B compliance)
 - Failure to meet the conditions of section 503B, such as
 - Failure to include appropriate labeling
 - Failure to submit required product reports

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Warning Letters

- Outsourcing facilities received about 20 of the 60 warning letters issued since October 2012
- Several of the outsourcing facilities that received warning letters subsequently deregistered with FDA
- Unapproved new drug and misbranding charges are included in warning letters to outsourcing facilities that fail to meet the conditions of section 503B

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 **Warning Letters: Examples**

- Some examples of deviations from adequate sterile practices and conditions cited in recent warning letters include:
 - Mold in unopened vials of purportedly sterile products
 - Production of sterile drugs with exposed skin
 - Failure to use a sporicidal agent to disinfect the ISO 5 area
 - No environmental monitoring during periods of sterile drug production
 - Use of non-sterile cleaning and disinfecting agents in aseptic processing areas

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 **State Referral Letters**

- State Referral Letters:
 - Sent to State Board of Pharmacy in the state in which the FDA-inspected compounding pharmacy is located when a
 - Pharmacy apparently compounds drugs in accordance with the provisions of section 503A (e.g., obtains prescriptions for identified individual patients); and
 - Pharmacy has promised to correct deviations, and they are readily correctable
 - FDA has issued approximately 20 state referral letters

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 **Injunctions**

- To prevent further production and/or distribution of adulterated, misbranded, and/or unapproved new drug products and to correct the root cause of the violations
- The firm has a history of significant violations and has not made corrections

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Injunction Process

- FDA drafts referral letter, complaint, and consent decree and submits to the Department of Justice (DOJ)
- DOJ determines whether to pursue the case
- May issue "sign or sue" letter
- Attempt to negotiate consent decree
- File complaint in court

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Compounding Injunction Cases Since 2012

- On June 28, 2013, a federal judge entered a consent decree of permanent injunction against MedPrep Consulting (Tinton Falls, NJ) and the company's president and owner.
- On December 4, 2014, a federal judge entered a consent decree of permanent injunction against Main Street Family Pharmacy (Newborn, TN) and the company's co-owners. In addition, Main Street and one of its co-owners pleaded guilty to a misdemeanor criminal violation of the FD&C Act.
- On March 10, 2015, a federal judge entered a consent decree of permanent injunction against Specialty Compounding (Cedar Park, TX) and the company's co-owners.
- The firms in each case manufactured purportedly sterile injectable drug products that tested positive for bacterial contamination.

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Compounding Criminal Cases Since 2012

- On December 16, 2014, a grand jury returned a 131-count criminal indictment in connection with the New England Compounding Center (NECC) and 2012 nationwide fungal meningitis outbreak. The owner and head pharmacist of NECC and its supervisory pharmacist were charged with 25 acts of second-degree murder, among other criminal acts, and 12 others were charged with additional crimes, including FDCA violations.
- On February 20, 2015, the Government unsealed a 37-count indictment charging Med Prep, its president and owner, and its pharmacist-in-charge, with wire fraud and violations of the FDCA for introducing adulterated and misbranded drugs into interstate commerce with the intent to defraud and mislead the FDA and Med Prep's customers.

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Sterile Drug Production Practices: USP <797> vs. CGMPs



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Summary of Presentation

- Fundamentals
- Facility design and qualification
- Environmental and personnel monitoring
- Equipment, containers and closures
- Components
- Production and process controls
- Laboratory control
- Beyond-use/expiration dating
- Quality assurance



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Drug Quality Attributes

- For injectables
 - **Sterility**
 - Endotoxin
 - Identity
 - Strength (a.k.a. Potency)
 - Purity
 - Other, for example:
 - Content uniformity
 - Anti-microbial effectiveness (if multiple dose container)



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Drug Quality Assurance

- Drug quality is built into the drug by paying attention to facility design and production process.
- Drug quality cannot be tested into the product.
 - Vast majority of all drug analytical testing is destructive.
 - Quality of non-tested units is inferred by test results, but not confirmed.
 - The ability of the test to infer quality of the non-tested unit is also dependent upon the quality attribute under assessment.

Sterility Tests

- *USP <71>* - *Sterility Tests*
 - Most commonly used and best understood
 - Detection method is based upon microbial proliferation

“These Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by validation of the sterilization process or of the aseptic processing procedures.” – from *USP <71>*



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Sterility Test Hypothetical

- 100 mL stock solution of drug X is prepared to produce a batch of 100, 1-mL vials.
- There is a breach in aseptic processing during production and, unknowingly, 10 colony-forming units (CFUs) are introduced into stock solution before filling into vials.



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Hypothetical

- If *USP <71>* sampling requirements are followed, 10 of 100 vials would undergo sterility tests.
- Statistically, even if you assume that the contamination is concentrated in the 10 vials tested at 1 CFU per vial, there's a 15% probability that the vials you pick will not be contaminated



Sterility Test Limitation

- Microbial contamination is highly unlikely to be equally distributed throughout the stock solution and actual distribution is unknown.
- In addition, no guarantees that all 10 CFUs will proliferate during sterility testing.
 - Some may be viable, but not cultivatable (VBNC).
- **Under actual testing conditions, probability of false negative is:**
 - **Higher than simple statistics would estimate and**
 - **Not calculable.**
- Ability of sterility test to detect contamination also decreases if:
 - Less than required (as per USP <71>) sample number is used
 - Drug formulation inherently inhibits microbial growth and no modification made in sample preparation to address

Sterility Test – Summary

- If contamination is identified, you have been alerted and can withhold lot. However:
- Ability of sterility tests to detect contamination is dependent upon:
 - Degree of microbial contamination (bioburden), which is unknown
 - Distribution of contamination through batch, which is unknown
 - Percentage of VBNC microbes, which is unknown
 - Number of samples taken from batch



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Sterility Assurance

Potential sources of microbial contamination:

- Air
- Water
- Equipment and supplies
- Drug components
 - Drug substances
 - Excipients
 - Container & Closures
- Personnel

Facility Design

- “Normal” air contains numerous suspended particles.
- Suspended particles contain unknown numbers of microbes adhering to particle surfaces.
- Design of firm must include built-in features that remove and control number of air particles in aseptic processing areas.



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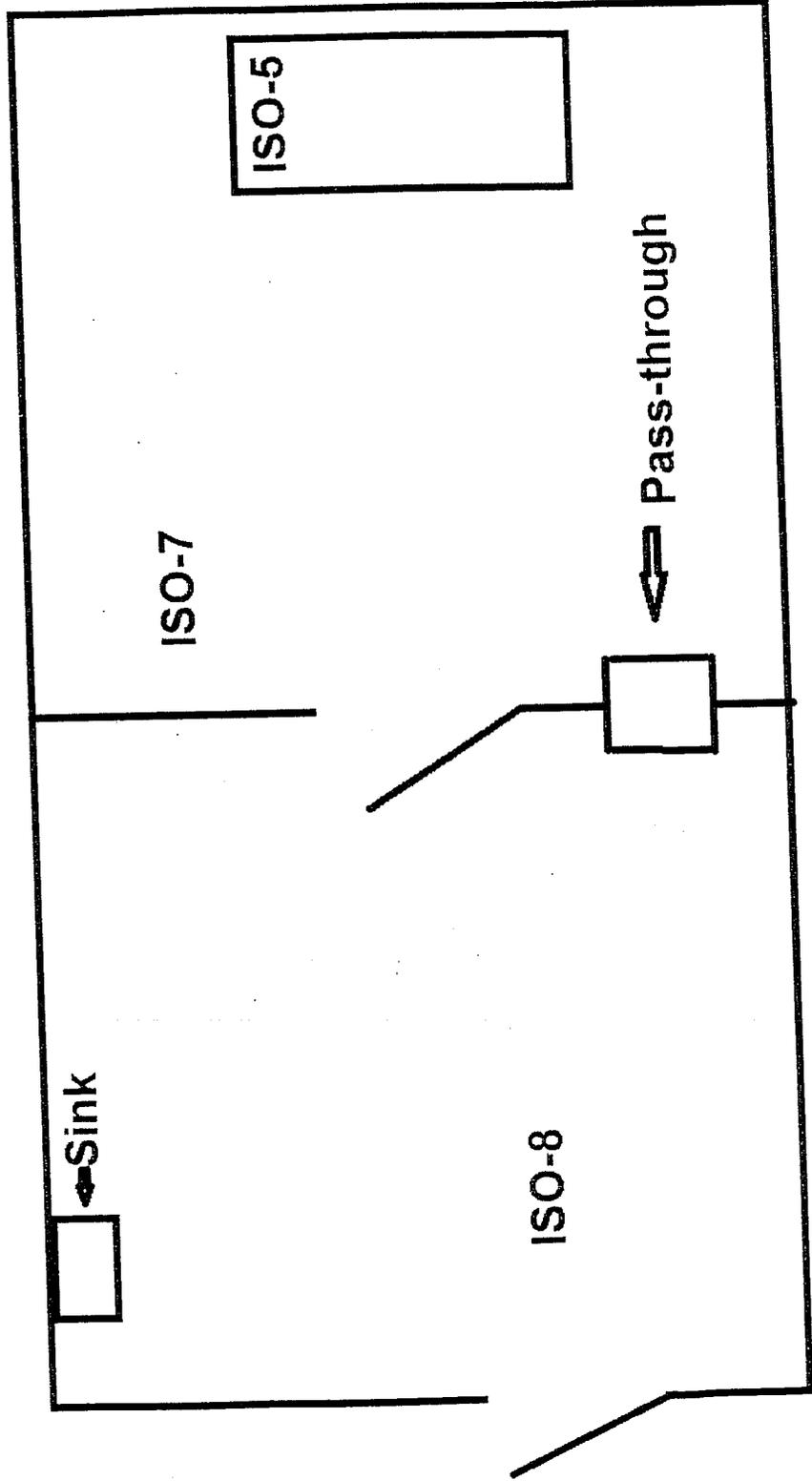
Air Cleanliness

- International Organization for Standardization (ISO) air cleanliness standards:
 - ISO-5: 3,520 particles of 0.5 $\mu\text{m}/\text{m}^3$
 - ISO-7: 352,000 particles of 0.5 $\mu\text{m}/\text{m}^3$
 - ISO-8: 3,520,000 particles of 0.5 $\mu\text{m}/\text{m}^3$
- Air cleanliness within a defined space is brought about by “high-efficiency particulate arrestance” (HEPA) filters incorporated at key location within a firm’s “heating, ventilation, and air-conditioning” (HVAC) system.



Basic Facility Design – Pharmacy

most common
design
for
Phy





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Qualification of ISO-5

<797>	Proposed <797>	CGMP
Yes	Yes	Yes
<u>Meet ISO-5 particle count</u>		
6 months	6 months	Continuously during production
<u>Frequency of monitoring/test</u>		
<u>Conditions of Test</u>		
Dynamic	Dynamic	Dynamic



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Qualification of ISO-5

CGMP

Proposed <797>

<797>

Demonstration of uni-directional air flow

Yes

Yes

Yes

Conditions of test

Dynamic

Dynamic

Dynamic



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Qualification of ISO-7 & 8

<797> Proposed <797> CGMP

Meet ISO-7/8 particle count

Yes Yes Yes

Frequency of monitoring/test

6 months 6 months Continuously during operations

Conditions of test

Dynamic Dynamic Dynamic

Demonstration of air-flow through and out of rooms

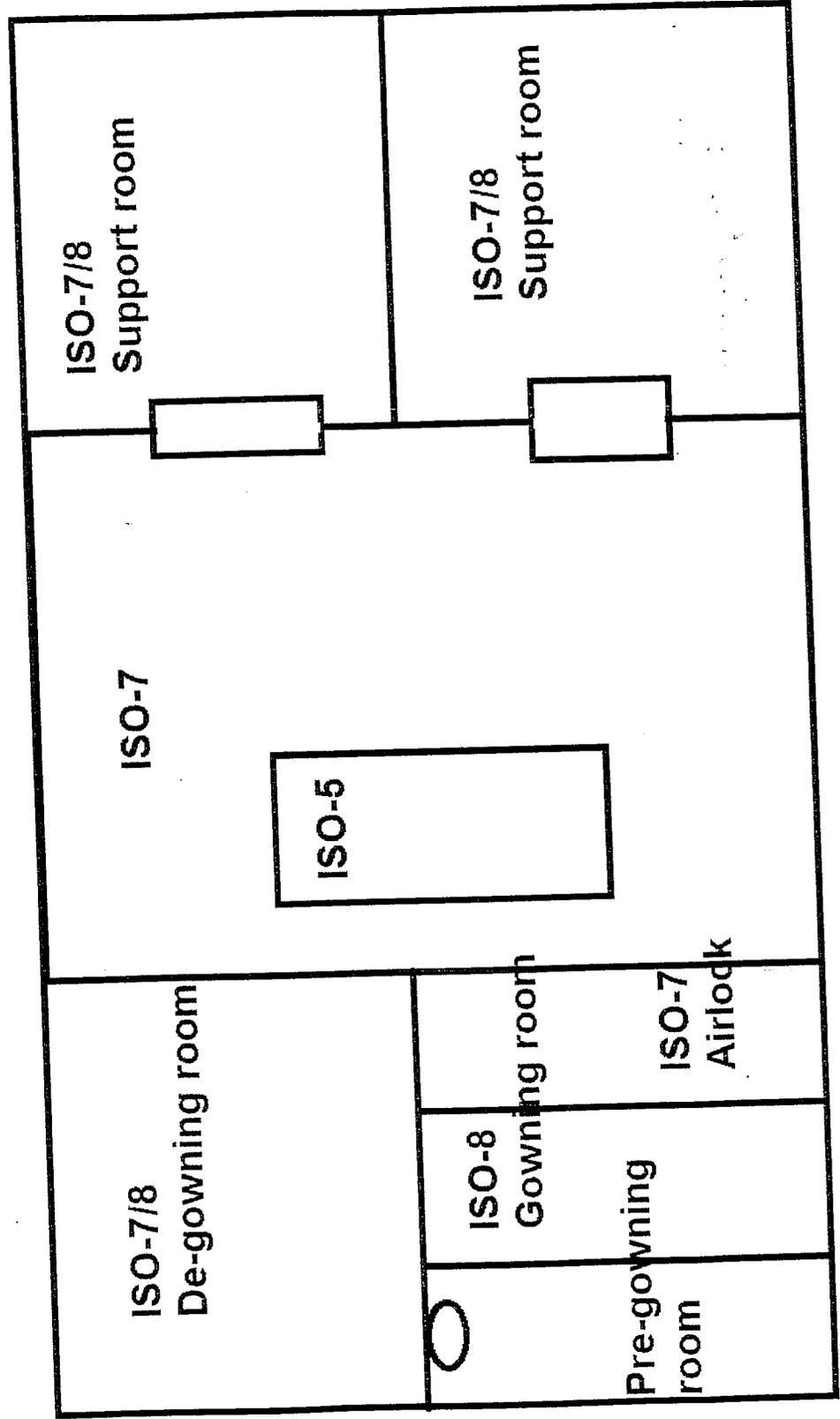
Not addressed Not addressed Recommended



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Design – Conventional Manufacturer





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*Non viablest determine there
is no thing living on
first media*

Environmental Monitoring Frequency

<797> Proposed <797> CGMP

Particle count (a.k.a. "non-viable air")

6 months 6 months Continuously during operation

Viable air particle

6 months 1 month Continuously during operation

Surfaces

6 months 1 month Multiple times during operation

Pressure differentials between rooms

Daily before production Daily before production Continuously during operation



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AVENUE 14851 1500V

Personnel Monitoring

CGMP

Proposed <797>

<797>

Frequency

Multiple times during operations

3 months

6 months

Area sampled

Gloved fingertips plus other, select areas of gown.

Gloved fingertips only

Gloved fingertips only



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Equipment, Containers and Closures

<797>

Proposed <797>

CGMP

Routine calibration of "measuring" equipment

Implied

Implied

Explicitly required

Ability of container-closures to maintain sterility

Assumed

Assumed

Required to be demonstrated



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Components

CGMP

Proposed <797>

<797>

Acceptance of incoming drug components

Review of COA plus
confirmatory testing

Review of COA

Review of COA

Determination of bioburden/endotoxin of incoming non-sterile ingredients

Required

Not required

Not required



Production and Process Controls - Gowning

<797> Proposed <797> CGMP

Required sterile gowning items

Gloves, only Gloves and sleeve covers, only Gloves and all other gowning items

Exposed skin?

Neck, checks, eyes, and forehead allowed. Wrist skin not allowed. Neck, checks, eyes, and forehead allowed. Wrist skin not allowed. None allowed

Reuse of gowning items?

Gloves and mask, no. Gloves, sleeve and mask, no. If other items sterile when first donned, then no. If other items were non-sterile when donned, then yes if stored in ISO-8 No



Production and Process Control – Sterilization and Maintenance of Sterility

<797> Proposed <797> CGMP

Filter sterilization

Acceptance of filter based upon certificate of suitability alone	Acceptance of filter based upon certificate of suitability alone	Need to confirm suitability of filter with actual product
--	--	---

Terminal sterilization

Process verified (no qualification of equipment required)	Process verified (no qualification of equipment required)	Process validated and includes qualification of equipment
---	---	---

Aseptic media fill simulation

“most challenging and stressful conditions” – no guidance given	“most difficult and challenging... conditions” – guidance given	Simulate actual process
---	---	-------------------------



Production and Process Control – Cleaning and Disinfecting

<797> Proposed <797> CGMP

Use of sterile cleaning and disinfecting agents/aids

Isopropanol required to be sterile, silent on all other agents/aids All agents/aids required to be sterile

Routine use of sporicidal agents

Recommended if EM data indicates presence of spore-forming microbes Required (weekly recommended)

Disinfecting agent efficacy studies

Not required Not required Required



Release/finished Product

Testing

CGMP

Proposed <797>

<797>

Sterility Tests

Not required, if default storage times (BUDs) are assigned	Not required, if default storage times (BUDs) are assigned	Required
--	--	----------

Endotoxin Test

Required only for CSPs made from non-sterile ingredient(s) and batch sizes of 26+ units	Required only for Category 2 CSPs made from non-sterile ingredient(s). Elimination of batch size requirement	Required
---	--	----------

Strength (potency) and other quality attribute tests

Not required	Not required	Required
--------------	--------------	----------



Laboratory Controls

<797> Proposed <797> CGMP

Sterility and Endotoxin Tests

Compliance with USP <71> and <85> Bacterial
Endotoxin Testing implied

Compliance with USP <71> and <85> Bacterial
Endotoxin Testing explicit
If <71> and <85> are used, then must comply with stated requirements.
If alternative methods are used, methods must be fully validated.



Beyond-use/expiration Dating

CGMP

Proposed <797>

<797>

Performance of stability tests

Not required, reliance on published literature	Required only for anti-microbial agent, if present. Otherwise, from published literature.	Required
--	---	----------

BUD/Expiry limits

Can be based solely upon published literature, no upper limits placed on BUDs	Upper limits placed on BUDs due to lesser sterility assurance compared to CGMP-compliant firms	Expiration date must be supported by comprehensive stability studies
---	--	--



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Quality Assurance

<797>

Proposed <797>

CGMP

Sterility and other quality failures – investigations

Recommended, not required. Silent regarding need to consider impact of failure on other products

Required. Investigation must be comprehensive and consider the impact of failure on other products

Required. Investigation must be comprehensive and consider the impact of failure on other products



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Questions?

Attachment 11

Director's Forum

USP <800>: Key Considerations and Changes for Health Systems

Priya Sahadeo, PharmD,* and Robert J. Weber, PharmD, MS, BCPS, FASHP†

On March 28, 2014, The United States Pharmacopeia and The National Formulary (USP-NF) published USP General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings, as open for public comment in the USP Pharmacopeial Forum (PF) 40(3). Pharmacy directors must be proactive in understanding the impact that USP <800> will have on their processes for preparing sterile products. USP General Chapter <797> pertains to the compounding of both hazardous and non-hazardous drugs. USP <800> serves as a new standard to guide the handling of hazardous drugs in order to protect patients, health care personnel, and the environment. USP <800> describes hazardous drug handling related to the receipt, storage, compounding, dispensing, administration, and disposal of both sterile and nonsterile products and preparations. Regardless of all of the requirements listed in USP <800>, there is no substitute for disciplined, consistent work practices regarding proper sterile technique. This point should be emphasized with all compounding personnel. Even if one is compounding in the most compliant USP <800> cleanroom, improper technique can negate all the benefits of the physical structures. Pharmacy leaders at every level will play a key role in assisting an organization to achieve timely compliance with USP <800> standards. Until the standard becomes official, it is important for pharmacists to become familiarized with the latest draft to identify potential barriers to compliance and to strategize a plan to overcome barriers. Although complying with USP <800> may seem to be a daunting task, it can be manageable if approached in a systematic organized way.

INTRODUCTION

The 2012 New England Compounding Center tragedy is well known; 678 confirmed cases of contaminated intravenous preparations resulted in over 60 deaths.¹ As the analysis of the tragedy unfolded, it was obvious that many of the deaths and disabilities could have been prevented if the center had adhered to fundamental guidelines of preparing sterile intravenous preparations. A call to action was generated by many professional organizations and groups to take the recommendations for compounding as set forth by The United States Pharmacopeia (USP) seriously. The authority of the US Food and Drug Administration (FDA) in regulating sterile compounding was reviewed, and accrediting organizations took a firm stand on institutions implementing the standards of USP General Chapter <797>. As a result, a 2014 National Survey of <797> standards

in hospitals showed increases in compliance with both sterile preparation and hazardous drug requirements – but there was room for significant improvement.²

On March 28, 2014, The United States Pharmacopeia and The National Formulary (USP-NF) published USP General Chapter <800> Hazardous Drugs—Handling in Healthcare Setting, as open for public comment in the USP Pharmacopeial Forum (PF) 40(3), the free online-only journal in which USP publishes revisions to USP-NF. The first round of public comments ended on July 31, 2014; these comments were incorporated by the USP Compounding Expert Committee into a revised chapter. The second round of public comments on the revised chapter opened on December 1, 2014 and closed on May 31, 2015. The official date of chapter publication has not been determined, but it is highly anticipated by

*PGY2 Pharmacy Administration Resident, †Administrator, Pharmacy Services, The Ohio State University Wexner Medical Center, Columbus, Ohio

stakeholders because this chapter requires key operational changes in the preparation of intravenous medications. Pharmacy directors must be proactive in understanding the impact that USP <800> will have on their processes for preparing sterile products.

The goal of this article is to provide a primer to pharmacy directors and others on new requirements and updates to hazardous drug handling as designated by USP <800>. This article will provide a brief overview of the USP, review the highlights of <800>, describe differences between USP <797> and USP <800>, and describe the impact that <800> will have on sterile compounding programs in health systems. Protecting the public by preventing harm from tainted sterile products is of paramount importance and is a fundamental step in providing patient-centered pharmacy services. Protecting personnel who are involved in the handling of hazardous drugs is just as important and should be given the attention it deserves.

THE UNITED STATES PHARMACOPEIAL CONVENTION

Overview

The United States Pharmacopeial Convention is a not-for-profit scientific organization that develops and publishes general chapters in order to provide the public with quality standards regarding drugs, excipients, and supplements.³ The standards include, but are not limited to, areas such as product identity, strength, quality, and purity. The value of these standards lies in the robust approval process for publication in the USP-NF. Although standards generally originate from sponsors, the supporting data that they provide is first reviewed by USP's scientific staff and volunteer experts; they then undergo rigorous public review and comment, followed by final approval from a USP Expert Committee. Six months after publication in the USP-NF, the standard becomes official and can be enforceable by the FDA and other agencies.

There are 5 USP-NF general chapters on compounding³: USP <795> Pharmaceutical Compounding–Nonsterile Preparations, USP <797> Pharmaceutical Compounding–Sterile Preparations, USP <1160> Pharmaceutical Calculations in Prescription Compounding, USP <1163> Quality Assurance in Pharmaceutical Compounding, and USP <1176> Prescription Balances & Volumetric Apparatus. As a general rule, chapters that are named with numbers under 1000 are enforceable and chapters named with numbers greater than 1000 are informational. Health system pharmacists are most likely familiar with USP <795> Pharmaceutical

Compounding–Nonsterile Preparations and USP <797> Pharmaceutical Compounding–Sterile Preparations. USP <797> is the standard by which to prevent harm and death to patients who are administered compounded sterile preparations (CSPs). USP <797> has undergone one revision that was published in 2008 and is currently undergoing a second revision, which was started in July 2010.⁴

USP <797>and USP <800>

The objective of USP <797> is “to prevent harm, including death to patients that could result from microbial contamination (nonsterility), excessive bacterial endotoxins, variability in the intended strength of correct ingredients, unintended physical or chemical contaminants and ingredients of inappropriate quality in CSPs.”⁴ USP <797> therefore focuses on the minimum practice and quality standards to ensure safe preparation of CSPs for patient use and is divided into sections such as responsibility of compounding personnel, personnel training and evaluation in aseptic manipulation skills, hazardous drugs as CSPs, verification of compounding accuracy and sterility, environmental quality and control, suggested standard operating procedures (SOPs), elements of quality control, finished preparation release checks and tests, storage and beyond use dating, maintaining sterility, purity and stability of dispensed and distributed CSPs, patient monitoring and adverse event reporting, and quality assurance program. These standards are important and, when upheld, can mitigate serious patient harm. The New England Compounding Center fatal meningitis outbreak of October 2012 resulted from noncompliance with compounding standards and highlighted the importance of compliance to scientifically tested practices and techniques as outlined in USP <797>.

USP <797> applies to the compounding of both hazardous and nonhazardous drugs. It defines a hazardous drug as one which studies in animals or humans indicate that exposures have a potential for causing cancer, development of reproductive toxicity, or harm to organs. USP <797> also recommends referring to the most updated National Institute for Occupational Safety and Health (NIOSH) List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings to identify whether a drug is classified as hazardous.⁵ A section within USP <797> titled “Hazardous Drugs as CSPs” addresses the risk of adverse effects to health care workers, general storage conditions of hazardous drugs, general

handling of hazardous drugs, allowable preparation hoods, recommended personal protective equipment (PPE), use of closed-system transfer devices (CSTDs), training of personnel handling hazardous drugs, routine environmental sampling, and improvement actions. The recommendations in this section provide a broad scope of guidance and do not offer in-depth recommendations on the areas listed above.

Although USP <797> provides guidelines for preparing sterile compounds, there is a need for defined standards related to the handling of hazardous drugs. Annually, there are over 8 million US health care personnel who are potentially exposed to hazardous medications.⁶ There have been various reports in the literature regarding the harmful effects of hazardous medications to health care workers, such as compromised reproductive health, increased risk for cancers, and a range of adverse effects including rashes, ocular problems, and headaches.⁷ Within the last 25 years, agencies such as Occupational Safety and Health Administration (OSHA) and NIOSH, as well as organizations such as the American Society of Health-System Pharmacists (ASHP), have addressed issues and provided guidance about handling hazardous drugs.

USP <800> Hazardous Drugs—Handling in Healthcare Settings serves as a new standard to protect patients, health care personnel, and the environment. USP <800> describes hazardous drug handling related to the receipt, storage, compounding, dispensing, administration, and disposal of both sterile and nonsterile products and preparations.

Who Can Enforce USP Standards?

USP is not an enforcement agency. State boards of pharmacy usually regulate the compounding practices of the organizations within their jurisdiction. Although boards of pharmacy do not delineate every compounding standard within their laws and rules, most boards have one blanket law that specifically mandates compliance with the USP's compounding general chapters. The FDA also has oversight over compounding and may legally enforce USP's compounding standards,⁸ however the FDA is perhaps most concerned with USP standards from the perspective of ensuring that compounded products are not adulterated from the standards set forth in their monographs. The Joint Commission on Accreditation of Healthcare Organizations has standards that are congruent with USP <797> principles. Even though The Joint Commission does not survey for compliance

with the details of USP <797>, USP standards can assist organizations in complying with relevant and applicable Joint Commission standards.⁹ It can reasonably be anticipated that The Joint Commission may take a similar approach to USP <800>.

HIGHLIGHTS FROM USP <800>

This article is not meant to be a comprehensive review of USP <800>, but rather a review of the most important aspects of these regulations.¹⁰ Pharmacy directors should have a general knowledge of the contents of <800>, along with a general knowledge of the differences between <800> and <797>.

Section 2: List of Hazardous Drugs

Section 2 lists the requirements for entities that should maintain an internal list of hazardous drugs. USP <800> does not provide a comprehensive list of hazardous drugs, but it references the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings. Entities can utilize NIOSH's criteria for identification of hazardous drugs when deciding to add drugs to their custom list, along with drugs already on the NIOSH list. Since 2012, NIOSH has updated their list biennially, with the next update anticipated in 2016. USP <800> requires that entities review their own lists at least annually, so this could provide a means by which to ensure that the NIOSH updates are considered each time. The finalized USP <800> may also require an update, as necessary, to the organization's list of hazardous drugs whenever a new agent or dosage form is used by the organization. However, this requirement may undergo wording changes based on the last round of feedback received. The intent of USP <800> seems to be to encourage entities to take a more conservative approach when there is uncertainty about the classification of a drug as hazardous.

The 2014 NIOSH update stratified drugs as antineoplastic, non-antineoplastic, and those that pose a reproductive risk. This stratification guides containment requirements as listed in Table 1.

Section 3 and 4: Types of Exposure and Responsibilities of Personnel Handling Hazardous Drugs

Sections 3 and 4 describe various routes of entry of hazardous drugs into the body, including exposure based on the type of activity being performed, such as dispensing, compounding, administration, patient care activities, spills, receipt, and transport. Section 4 has a unique requirement for entities to designate

Table 1. Containment requirements guide

Antineoplastic hazardous drugs		Non-antineoplastic hazardous drugs and drugs that pose a reproductive risk
Require manipulation	Do not require further manipulation other than counting dosage forms	
Must follow containment requirements outlined in USP <800>	Follow containment requirements per manufacturer or conduct an internal assessment of risk to determine if alternative containment strategies are necessary	Perform and document an internal assessment of risk to determine if alternative containment strategies are necessary

a Compounding Supervisor who is qualified and trained to be responsible for all aspects of hazardous drug handling, including, but not limited to, the development and implementation of procedures; compliance with laws, regulations, and standards; personnel competency; and environmental control. USP <800> provides no guidelines as to the credentials of the compounding supervisor nor whether the person has to be a pharmacy employee (pharmacist or pharmacy technician). However, it can be reasonably expected that both organizational leaders and hospital pharmacy leaders would prefer this position to be within the pharmacy department. Pharmacy leaders may choose to create a new position for this compounding supervisor or assign these responsibilities to an existing position within the department.

Section 5: Facilities

Section 5 is separated into 4 sections: receipt, storage, compounding, and containment supplemental engineering controls. *Receipt* refers to the unpacking of the drug from its original shipping containers; this must be done in a neutral/normal pressure or a negative pressure room to prevent the dispersal of any hazardous drug contamination on the packaging. Drugs cannot be unpacked in sterile compounding areas or positive pressure areas. The anteroom to a

negative pressure room is usually always a positive pressure room, so care must be taken to ensure no drugs are unpacked in this area. This requirement can present challenges, as a dedicated space for unpacking that meets these requirements has to be found.

USP <800> section on *storage* presents a change from the guidance of USP <797>. USP <797> states that hazardous drugs shall be stored separately from other inventory in a manner to prevent contamination and personnel exposure.⁴ USP <800> recognizes the 2014 NIOSH stratification of hazardous drugs and reflects this in its storage requirements, as depicted in **Table 2**. Of note, USP <800> allows sterile and non-sterile hazardous drugs to be stored together, but only sterile hazardous drugs may be stored in a negative pressure buffer room. If the sterile drug is an antineoplastic that requires manipulation, it must be stored in a negative pressure buffer area anyway.

USP <800> section on *compounding* is subdivided into nonsterile compounding and sterile compounding. It describes the classification of engineering controls as primary (containment primary engineering control or C-PEC or the hood), secondary (containment secondary engineering control or C-SEC or the room in which the C-PEC is contained), and supplemental or adjunct controls that offer additional levels of protection (eg, CSTDs).

Table 2. Storage requirements guide

Hazardous drugs that can be stored with other nonhazardous drug inventory	Hazardous drugs that must be stored separately from other nonhazardous drugs
<ul style="list-style-type: none"> • Non-antineoplastic hazardous drugs • Reproductive risk–only hazardous drugs • Final dosage forms of antineoplastic hazardous drugs 	Antineoplastic drugs or hazardous drugs API requiring manipulation other than counting final dosage forms: store in a negative pressure room with at least 12 air changes per hour (ACPH)
	Refrigerated antineoplastic hazardous drugs: store in a dedicated refrigerator in a negative pressure area with at least 12 ACPH

Note: API = active pharmaceutical ingredient.

For nonsterile hazardous drug compounding, the C-PEC should be externally vented or redundant HEPA filtered in series and must be placed in a C-SEC that has at least 12 ACPH. If a C-PEC is used solely for nonsterile compounding, unidirectional flow is unnecessary. Additionally, a C-PEC that is used for sterile compounding may be used for nonsterile compounding, but it must be properly decontaminated and disinfected before sterile compounding is resumed.

For sterile hazardous drug compounding, the C-PEC must provide a Class 5 or superior air quality and must be externally vented. By these requirements, a laminar airflow workbench (LAFW) or compounding aseptic isolator (CAI) should not be used for such compounding. USP <800> requires that the C-PEC be contained within a C-SEC that is an ISO Class 7 buffer room or an unclassified containment segregated compounding area (C-SCA). A C-SCA is a type of C-SEC with nominal requirements for airflow and room pressurization in that it is ISO unclassified but is a segregated room that maintains negative pressure and is externally vented with at least 12 ACPH. The only sterile hazardous drugs that may be prepared in a C-SCA are low- and medium-risk drugs. A C-SCA is a less expensive option to an ISO-classified, negative pressure cleanroom and provides allowance for compounding of hazardous drugs in clinics that do not have negative pressure cleanroom infrastructure, which is often the case for many outpatient settings. However, if a drug is compounded in a C-SCA, the beyond use date (BUD) will be limited to 12 hours to offer protection to the patients from microbial contamination. The requirement described above is a stricter requirement from USP <797>, which allowed a small volume of hazardous drugs to be compounded in a C-PEC located in a non-negative pressure room. Additionally, USP <800> outlines requirements for maintaining an ISO Class 7 buffer room, as well as requirements for a line of demarcation and transport procedures when the entrance to an ISO Class 7 buffer room is a positive pressure nonhazardous drug buffer room.

USP <800>'s requirements with respect to CSTDs are also different from USP <797>. Whereas USP <797> recommended the use of CSTDs, USP <800> mandates that they be used both for compounding and administering once the dosage form allows. Examples of dosage forms that may not allow the use of CSTDs include intrathecal, ophthalmic, and irrigations. This is a very significant change as it may affect entities that currently do not use CSTDs. These devices are more expensive than traditional

needle and syringe compounding equipment. There are currently no universal performance standards for CSTDs. USP <800> enforcement will favor the market for CSTDs, so more stringent device regulation will be necessary to ensure quality control from existing and potential manufacturers. Furthermore, when contracting the purchase of a CSTD product from a vendor, each entity should consider device effectiveness, nursing input, and pharmacy input.

Section 6: Environmental Quality and Control

Section 6 describes surface wipe sampling and states that it should be performed at least every 6 months. There are currently no certifying agencies for the vendors of wipe kits nor set standards for acceptable limits of surface contamination with hazardous drugs. This is an area for future improvement. If contamination is measured, the compounding supervisor must document and contain the contamination, then take specific actions to reassess areas for improvement such as personnel retraining and improvement of engineering controls.

Section 7: Personal Protective Equipment

Section 7 gives specific and thorough guidance on gloves, gowns, head, hair, shoe and sleeve covers, eye and face protection, respiratory protection, and disposal of used PPE. Certain requirements are specifically stated:

- Compounding sterile and nonsterile hazardous drugs: Use gloves, gowns, head, hair and shoe covers.
- Administering antineoplastic hazardous drugs: Use gloves.
- Administering injectable hazardous drugs: Use gloves and gowns.

When handling antineoplastic hazardous drugs, double gloves must be worn; these gloves must have been tested for permeability according to the American Society for Testing and Materials (ASTM) standard D6978. Similarly, a second set of shoe covers must be donned when an individual enters the hazardous drug compounding area or C-SEC, and then removed upon exiting; this can be a tedious task for personnel who move between the negative pressure room to the anteroom. For all other activities, the entity must state their PPE requirements based on exposure risk and type of handling of hazardous drugs, including receipt, storage, transport, compounding, administration, deactivation/decontamination, cleaning, disinfecting, and spill control.

Sections 8, 9, and 10

Sections 8, 9, and 10, Hazard Communication Program, Personnel Training, and Receiving, contain important information. Section 8 refers to the requirement of entities to establish policies and procedures to ensure worker safety during hazardous drug handling. Such policies should include training on labeling, transport, storage, and use of easily accessible Safety Data Sheets (SDS) for every hazardous chemical used. Section 9 lists minimum areas of training for all personnel who handle hazardous drugs and requires that these individuals be fully trained and demonstrate competency before they independently handle hazardous drugs. Reassessment of competency must be performed and documented at least every 12 months, with the introduction of a new hazardous drug or equipment, and when a significant change in process occurs. Section 10 specifies that hazardous drugs must be received from the supplier sealed in impervious plastic and delivered immediately to the hazardous drug storage area. This section also mandates that PPE be worn, including tested, power-free chemotherapy gloves. There are clear instructions on how to handle damaged shipping containers and product, including containment, return, disposal, retrieval of usable items from a container with damaged items, and reporting procedures.

Sections 11 through 14

These sections (Labeling, Packaging, and Transport; Dispensing Final Dosage Forms; Compounding; and Administering) address key considerations in the logistics of hazardous drug safety. When a hazardous drug is in transit, it must be clearly labeled so as to be easily identifiable as such, at all times. Packaging containers should be carefully chosen on the basis of physical integrity, stability, sterility, and protection from damage, leakage, contamination, and degradation. The section on transport encourages compliance with relevant federal, state, and local regulations. It also cautions firmly against the use of a pneumatic tube system to transport any liquid hazardous drug and any antineoplastic hazardous drug due to breakage and contamination risks. Furthermore, clean designated equipment should be used when dispensing final dosage forms that do not require further manipulation. In light of the increasing use of automation by many hospital pharmacies, the following guidance is also very pertinent: Tablet and capsule forms should not be placed in automated

counting or packaging machines, because stress on the dosage forms can introduce powdered contamination into the equipment. Compounding of hazardous drugs must follow the standards within USP <795> and <797>, and compounding equipment must be designated and not intermixed for compounding of nonhazardous drugs. Additionally, section 13 urges the utilization of commercially available products as starting ingredients instead of crushing tablets, opening capsules, and using active pharmaceutical ingredients (APIs). The section on administration guides the use of PPE for administering hazardous drugs and recommends the use of protective techniques and ancillary devices when applicable. This section also lists the Oncology Nursing Society Safe Handling of Hazardous Drugs publication as a valuable resource on hazardous drug administration.

Sections 15 through 18

Sections 15 through 18 (Deactivation/Decontamination, Cleaning and Disinfection; Spill Control; Disposal; Documentation and Standard Operating Procedures) provide very detailed and specific guidance for the use of PPE for such activities, as well as definitions of and agents to be used in each cleaning step, including the use of combination agents (cleaning steps: deactivation, decontamination, cleaning, and disinfection). This guidance directs when cleaning should occur, lists techniques for wiping, and gives guidance on when and how to clean areas under the work tray of a C-PEC. The section on spill control stresses the importance of quick and easy access to a spill kit, signs for restricting access to the area, documentation of the circumstances and management of the spill, and immediate medical evaluation of anyone who has had direct skin or eye contact with hazardous drugs. Only qualified personnel wearing PPE should be involved in spill containment. Section 16 mandates that SOPs be developed for spill prevention and containment, but it does not provide detailed guidance on the content of spill kits nor guidance on appropriate training of personnel for spill management. The disposal section urges compliance with applicable federal, state, and local laws pertaining to hazardous drug waste; it is important for pharmacy leaders to be up to date with such regulations. The documentation and standard operating procedures section provides guidance on which activities must be documented and the content that must be included in the SOPs for the safe handling of hazardous drugs.

Section 19: Medical Surveillance

Section 19 addresses the medical surveillance program, the purpose of which is to minimize adverse health effects in persons potentially exposed to hazardous drugs. The concept of medical surveillance is based on a proactive approach for early detection of health problems that compares trends over time with an employee's baseline health status. This involves tracking of personnel via assessments and documentation of symptom complaints, physical findings, and laboratory values in order to assess deviations from norms and changes over time. It can also provide a means by which to determine population health trends among exposed personnel compared to unexposed personnel; this can be very helpful in determining the significance of findings. Section 19 discusses elements that should be contained in the entity's medical surveillance program, such as creating an organized approach for identifying potentially exposed workers, the importance of confidentiality and maintenance of health records, and follow-up plans for workers who have shown health changes related to toxicity. Although this section provides criteria that can be used to assess exposure history, it does not provide guidance for determining what a high exposure is nor how this information should be interpreted. For example, it suggests using an estimate of the number of hazardous drug preparations/administrations a health care worker performs in a week; however, there is no "acceptable" number for comparison and evaluation. The mandates within this section present significant changes from <797>, especially concerning confidentiality of health records and continuous monitoring. Employees may not feel comfortable with their health information being managed by someone working within their department, so this sensitive information may have to be interpreted by a separate party such as employee health personnel or a separate contracted agency.

IMPACT OF USP <800> ON HEALTH SYSTEM PHARMACY

Executive leadership support from the organizational entity, as well as the pharmacy department, will be instrumental to ensure timely compliance with USP <800>. This standard is broad and all-encompassing and can be legally enforced at both the federal and state levels. Other agencies, such as The Joint Commission and Centers for Medicare and Medicaid Services (CMS), may also request compliance with USP <800> standards. As such,

the impact of these standards on the organization is large and deserves the attention of all necessary stakeholders.

Most pharmacy leaders will agree that they have an unspoken duty to reasonably ensure the safety and protection of their employees. Leaders are looked to for guidance in times of change. As such, they have a responsibility to know the contents of the standard, be able to decipher and analyze it, and lead strategies to uphold it.

Leaders should be proactive in strategizing their organization's compliance with the standards. This will help eliminate unexpected barriers. A team of pharmacy experts in supply chain management, compounding, hazardous drugs (such as oncology pharmacists), and pharmacy administration should perform a gap analysis to identify areas that need special attention. For example, the entity's list of hazardous drugs should be updated, and its facilities should be evaluated for necessary modifications. It is important to make modifications in such a way as to minimize interruptions to ongoing pharmacy operations, as it is important to continue to provide care to patients.

Some other areas that will need to be analyzed include the adequacy of PPE used by individuals who manipulate hazardous drugs, retraining of personnel with documentation of competencies, and the creation or updating of SOPs. Education will be a big project; not only will pharmacy personnel need to be updated, but also nurses, physicians, risk management, legal, and drug delivery personnel from contracted suppliers. The process by which a hazardous drug is delivered to an institution until that drug is safely administered to a patient consists of many steps. It is important that there is tight control at each step in this pathway, along with safeguards to prevent unintended consequences. USP <800> is intended to provide exactly this standardized guidance. If an organization upholds standards throughout the entire process except for one step, then that entity can be considered noncompliant. It is advisable for organizations to provide feedback to USP, even after the standard has been finalized and enforcement has begun. It would also be helpful for separate entities to network and share information on strategies that have worked or not worked and to publish scientific research in this area where possible. There are areas where scientific evidence is lacking and research would greatly assist to streamline recommendations and even redefine standards within USP <800>.

Implementing USP <800> will increase the safety of preparing hazardous drugs, but there will be challenges to compliance. Table 3 lists some challenges along with some recommended strategies.

Regardless of all of the requirements listed in USP <800>, there is no substitute for disciplined, consistent work practices regarding proper sterile technique. This point should be emphasized with all compounding personnel. Even if one is compounding in the most compliant USP <800> cleanroom, improper technique can negate all the benefits of the physical structures.

Additionally, not all changes have to be implemented at once. Having a defined strategy that addresses the parts of USP <800> that are easily implemented is key to achieving success with USP <800> compliance. Many entities are still attempting to achieve compliance with the standards set forth in USP <797>,² so this impending guidance can make it even more difficult for them to keep abreast of changes. However, health systems should view it as an opportunity to target compliance with both standards in one combined effort. For example, if

facilities need to make changes to comply with USP <800>, then it would be wise for them to make any additional necessary updates that would also ensure compliance with USP <797>.

CONCLUSION

USP <800> is a standard that consolidates existing recommendations for handling hazardous drugs into one universally recognized reference. This standard will require many key operational changes for health systems and will have a far-reaching impact for maintaining patient care standards and health care employee safety and protection. Pharmacy leaders at every level will play a key role in helping organizations achieve timely compliance with USP <800> standards. Until the standard becomes official, it is important for pharmacists to become familiar with the latest draft, identify potential barriers to compliance, and strategize a plan to overcome barriers. Although complying with USP <800> may seem to be a daunting task, it can be manageable if approached in a systematic organized way.

Table 3. USP <800> compliance challenges and corresponding readiness strategies

Potential compliance challenges ¹¹	Strategies for USP <800> readiness
Financial and budgetary restrictions	<ul style="list-style-type: none"> • Conduct a gap analysis • Prioritize projects according to feasibility, ease of execution, and resource sharing amongst departments
Physical plant limitations	<ul style="list-style-type: none"> • Involve facilities engineering in plan for redesigning clean rooms
Training and competency	<ul style="list-style-type: none"> • Identify areas where retraining is needed • Rewrite policies and procedures
Resource availability	<ul style="list-style-type: none"> • Form partnerships among departments within the health system • Form partnerships among nearby hospitals • Consider the possibility of outsourcing
Time	<ul style="list-style-type: none"> • Strategize from early on, not when the standard has been published • Focus on areas in which a change in the final guideline will not require a serious overhaul
Resistance to change	<ul style="list-style-type: none"> • Prepare for change management • Maintain staff morale • Manage expectations • Foster teamwork
Lack of support and awareness from executive leadership	<ul style="list-style-type: none"> • Educate on USP <800> especially on risks of noncompliance • Seek buy-in from an early stage • Leverage “culture of safety” principles

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Attachment 12



California State Board of Pharmacy

1625 N. Market Blvd, N219, Sacramento, CA 95834

Phone: (916) 574-7900

Fax: (916) 574-8618

www.pharmacy.ca.gov

BUSINESS, CONSUMER SERVICES AND HOUSING AGENCY

DEPARTMENT OF CONSUMER AFFAIRS

GOVERNOR EDMUND G. BROWN JR.

**STATE BOARD OF PHARMACY
DEPARTMENT OF CONSUMER AFFAIRS
ENFORCEMENT AND COMPOUNDING COMMITTEE
MEETING MINUTES**

DATE: December 14, 2015

LOCATION: DCA Headquarters, First Floor Hearing Room
1625 North Market Blvd.
Sacramento, CA 95834

COMMITTEE MEMBERS

PRESENT: Amy Gutierrez, PharmD, Chair, Professional Member
Greg Lippe, Public Member, Vice Chair
Allan Schaad, Professional Member
Rosalyn Hackworth, Public Member

COMMITTEE MEMBERS

NOT PRESENT: Greg Murphy, Public Member
Stan Weisser, Professional Member

STAFF

PRESENT: Virginia Herold, Executive Officer
Anne Sodergren, Assistant Executive Officer
Janice Dang, PharmD, Supervising Inspector
Laura Freedman, DCA Staff Counsel
Rob Buckner, Investigations Manager
Laura Hendricks, Administrative Analyst

Call to Order

Dr. Gutierrez, chair of the committee, called the meeting to order at 10:15 a.m.

Dr. Gutierrez welcomed those in attendance. Roll call of the board members present was taken and a quorum of the committee was established.

I. PUBLIC COMMENT FOR ITEMS NOT ON THE AGENDA/AGENDA ITEMS FOR FUTURE MEETINGS

Holly Strom, representing the Institute for Community Pharmacy and the Los Angeles County Safe Opioid Prescribing Coalition, requested that the committee add an agenda item to a future committee meeting to discuss the Sternberg case and its relevance and the implications relating to the role of the Pharmacist in Charge (PIC). She also suggested that various scenarios be discussed to aid PICs in understanding their role.

Steve Gray, representing the Institute for Community Pharmacy, expressed concern that the Sternberg case was being touted as a strict liability case. He stated that the board's interpretation could create problems in recruiting and retaining PICs.

Bill Maguire, representing Omnicell, requested that the board consider allowing automated delivery devices in post-acute care settings and provide clarity on the locations where the devices can be used.

Megan Maddox, representing the California Pharmacists Association, requested that the board add an agenda item to a future meeting to discuss the topic of compounding pellets in an ISO 5 as a possible hazard.

II. ENFORCEMENT MATTERS

a. Presentation by the California Department of Health Care Services on California's Drug Utilization Review Program and the Medi-Cal DUR Educational Bulletin on "Morphine Equivalent Daily Dose to Prevent Opioid Overdose"

Background

There is housed in the California Department of Health Care Services a Drug Utilization Review Committee that supports the state's Medi-Cal program in creating drug benefits. Board Member Allen Schaad has asked that this program provide an overview of its duties and functions to the board's Enforcement and Compounding Committee, this will occur during this meeting. There will be three presentations as part of this segment.

- Pauline Chan, R.Ph., MBA, California Department of Health Care Services
- Shal Lynch, PharmD, CGP, Health Sciences Associate Clinical Professor
UCSF Department of Clinical Pharmacy, School of Pharmacy
- Randall S. Stafford, MD, PhD, Medi-Cal DUR Board Member, Professor of Medicine, Stanford University

Each day in the United States, 46 people die from an overdose of prescription opioid or narcotic pain relievers. Recent studies demonstrate that a patient's cumulative MEDD is an indicator of potential dose-related risk for adverse drug reactions to opioids, including overdose. As a result, many state Medicaid Drug Utilization Review (DUR) programs have established recommendations for MEDD or opioid dose limitation.

Discussion and Comment

At this meeting, Pauline Chan of the California Department of Health Care Services provided an overview of the Medi-Cal DUR program, and discussed the Medi-Cal DUR educational bulletin “Morphine Equivalent Daily Dose to Prevent Opioid Overdose.” The committee also heard a second presentation from Shal Lynch of the University of California, San Francisco regarding the evaluation of morphine equivalent daily dose (MEDD) in patient care.

Ms. Herold mentioned that one of the red flags for opioid misuse is cash payments. She asked Ms. Lynch whether there is any plan to match fee for service data to the CURES data in order to track transactions in which a patient uses Medi-Cal to pay for one prescription then uses cash to pay for others. Ms. Chan answered they are looking into integrating CURES data.

Dr. Gutierrez asked whether health plans are required to track MEDD. Ms. Chan stated some health plans had asked for MEDD information that they could use but that tracking MEDD is not required.

Dr. Gutierrez also asked whether Medi-Cal takes any action if a patient exceeds the California MEDD limit of 80mg. Ms. Chan and Ms. Lynch stated that the 80mg cutoff acts as a warning trigger but that no action is currently taken when a patient exceeds the MEDD.

There were no public comments.

Committee Recommendation:

Motion: Add the MEDD educational bulletin to the board’s website.

M/S: Lippe/Hackworth

Support: 4 Oppose: 0 Abstain: 0

b. Legislative Proposal for the Board of Pharmacy to Establish a List of Synthetic Cannabinoids that Would be Illegal for Use in California

Background

Spice (synthetic cannabinoids) and *bath salts* (synthetic cathinones) refer to two groups of designer drugs that have increased in popularity in recent years. These substances are created with *analogs* of commonly used illicit drugs. An analog is one of a group of chemical compounds that are similar in structure and pharmacology.

A form of synthetic cannabinoids, commonly referred to as “Spice” or “K2,” is designed to affect the body in a manner similar to marijuana, but is not derived from the marijuana plant. These substances began appearing across the U.S. in 2008, and their popularity grew over the following years mainly because they could be sold legally and not detected in urinalysis drug tests.

These substances contain different ingredients that have been reported to cause a number of physical reactions including agitation, anxiety, nausea, vomiting, tachycardia, elevated blood pressure, tremors, seizures, hallucinations, paranoid behavior, and no responsiveness. Synthetic cannabinoids are not currently identified using routine screening tests, and the creation of new products of this type makes it difficult to detect these chemicals or regulate products that contain these substances.

Although these substances were made illegal nationally in 2012, synthetic cannabinoids and cathinones remain available, generally through black market internet sites, indicating a need for continued education, prevention, and enforcement.

Young adults and youth are often the buyers.

California's Health and Safety Code as amended effective 1/1/16 provides the following:

11375.5. [Stimulants]

- (a) Every person who sells, dispenses, distributes, furnishes, administers, or gives, or offers to sell, dispense, distribute, furnish, administer, or give, any synthetic stimulant compound specified in subdivision (c), or any synthetic stimulant derivative, to any person, or who possesses that compound or derivative for sale, is guilty of a misdemeanor, punishable by imprisonment in a county jail not to exceed six months, or by a fine not to exceed one thousand dollars (\$1,000), or by both that fine and imprisonment.
- (b) Every person who uses or possesses any synthetic stimulant compound specified in subdivision (c), or any synthetic stimulant derivative, is guilty *of-an infraction, punishable by a fine not to exceed two hundred fifty dollars (\$250).*
- (c) Unless specifically excepted, or contained within a pharmaceutical product approved by the United States Food and Drug Administration, or unless listed in another schedule, subdivisions (a) and (b) apply to any material, compound, mixture, or preparation which contains any quantity of a substance, including its salts, isomers, esters, or ethers, and salts of isomers, esters, or ethers whenever the existence of such salts, isomers, esters, or ethers, and salts of isomers, esters, or ethers is possible, that is structurally derived from 2-amino-1-phenyl-1-propanone by modification in one of the following ways:
 - (1) By substitution in the phenyl ring to any extent with alkyl, alkoxy, alkylendioxy, haloalkyl, or halide substituents, whether or not further substituted in the phenyl ring by one or more other univalent substituents.
 - (2) By substitution at the 3-position with an alkyl substituent.
 - (3) By substitution at the nitrogen atom with alkyl or dialkyl groups, or by inclusion of the nitrogen atom in a cyclic structure.
- (d) This section shall not prohibit prosecution under any other provision of law.

And

11357.5. [Synthetic Cannabinoids]

- (a) Every person who sells, dispenses, distributes, furnishes, administers, or gives, or offers to sell, dispense, distribute, furnish, administer, or give, or possesses for sale any synthetic cannabinoid compound, or any synthetic cannabinoid derivative, to any person, is guilty of a misdemeanor, punishable by imprisonment in a county jail not to exceed six months, or by a fine not to exceed one thousand dollars (\$1,000), or by both that fine and imprisonment.
- (b) Every person who uses or possesses any synthetic cannabinoid compound, or any synthetic cannabinoid derivative, is guilty of an infraction, punishable by a fine not to exceed two hundred fifty dollars (\$250).
- (c) As used in this section, the term “synthetic cannabinoid compound” refers to any of the following substances:
 - (1) Adamantoylindoles or adamantoylindazoles, which includes adamantyl carboxamide indoles and adamantyl carboxamide indazoles, or any compound structurally derived from 3-(1-adamantoyl)indole, 3-(1-adamantoyl)indazole, 3-(2-adamantoyl)indole, N-(1-adamantyl)-1H-indole-3-carboxamide, or N-(1-adamantyl)-1H-indazole-3-carboxamide by substitution at the nitrogen atom of the indole or indazole ring with alkyl, haloalkyl, alkenyl, cyanoalkyl, hydroxyalkyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidinyl)methyl, 2-(4-morpholinyl)ethyl, or 1-(N-methyl-2-pyrrolidinyl)methyl, 1-(N-methyl-3-morpholinyl)methyl, or (tetrahydropyran-4-yl)methyl group, whether or not further substituted in the indole or indazole ring to any extent and whether or not substituted in the adamantyl ring to any extent, including, but not limited to, 2NE1, 5F-AKB-48, AB-001, AKB-48, AM-1248, JWH-018 adamantyl carboxamide, STS-135.
 - (2) Benzoylindoles, which includes any compound structurally derived from a 3-(benzoyl)indole structure with substitution at the nitrogen atom of the indole ring with alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidinyl)methyl, 2-(4-morpholinyl)ethyl, or 1-(N-methyl-2-pyrrolidinyl)methyl, 1-(N-methyl-3-morpholinyl)methyl, or (tetrahydropyran-4-yl)methyl group, whether or not further substituted in the indole ring to any extent and whether or not substituted in the phenyl ring to any extent, including, but not limited to, AM-630, AM-661, AM-679, AM-694, AM-1241, AM-2233, RCS-4, WIN 48,098 (Pravadoline).
 - (3) Cyclohexylphenols, which includes any compound structurally derived from 2-(3-hydroxycyclohexyl)phenol by substitution at the 5-position of the phenolic ring by alkyl, haloalkyl, cyanoalkyl, hydroxyalkyl, alkenyl, cycloalkylmethyl, cycloalkylethyl, 1-(N-methyl-2-piperidinyl)methyl, 2-(4-morpholinyl)ethyl, or 1-(N-methyl-2-pyrrolidinyl)methyl, 1-(N-methyl-3-morpholinyl)methyl, or (tetrahydropyran-4-yl)methyl group, whether or not further substituted in the cyclohexyl ring to any extent, including, but not limited to, CP 47,497, CP 55,490, CP 55,940, CP 56,667, cannabicyclohexanol.

And more of this follows in the section.

Discussion and Comment

At this meeting, the committee reviewed and discussed a legislative concept that would be authored as 2016 legislation by Senator Hernandez to have the Board of Pharmacy establish a list of synthetic cannabinoids and stimulants that would be illegal for use in California until incorporated formally as statutory modifications into Health and Safety Code sections 11375.5 and 11357.5. Currently the Senator's office is working on the language.

Ms. Herold explained that the Controlled Substances Act is very specific. Because it is so specific about the type of substances that are illegal, one molecule of the substance can be changed and the substance becomes legal. The process to address the new substance and make it illegal by adding it to statute is long and complicated. Therefore, Senator Hernandez wants to find a way by which the board could provide an interim step, perhaps by emergency, short term regulations. This would allow law enforcement to use the board's regulation to arrest and prosecute vendors while the Department of Justice seeks revisions to the permanent statute.

The board heard comments from an individual who provided an article on Synthetic Marijuana Linked to Major Birth Defects and also asked how a pharmacist is supposed to provide patient consultation to an individual who is also taking medical marijuana. Dr. Gutierrez indicated that the item was not on the agenda and asked the commenter to keep her comments focused on cannabinoids or pending legislation. The commenter indicated she is in favor of the board working with Senator Hernandez's office.

Committee Recommendation:

Motion: Work with Senator Hernandez to develop the legislative concept.

M/S: Lippe/Hackworth

Support: 4 Oppose: 0 Abstain: 0

c. Update by the University of California, San Diego on Its Pilot Program to Permit Patients to Access Medication from an Automated Storage Device not Immediately Adjacent to a Pharmacy

Background

At the Board of Pharmacy's April 2015 Board Meeting, the board approved an 18-month pilot study under the auspices of the UCSD School of Pharmacy. The study involves the use of an automated storage device from which staff and their families of a Sharp Hospital in San Diego, who opt in, may pick up their outpatient medications. This device will be located in a hospital and should be more convenient for employees than having to go to a community pharmacy. Consultation will be provided via telephone before medication can be dispensed to a patient.

This study was planned to start in June or July, 2015; however, at the September 9, 2015 Enforcement Committee meeting, Dr. Jan Hirsch, BS Pharm, PhD, spoke via telephone and anticipated the pilot study would not begin until December.

Discussion and Comment

At this meeting, Dr. Hirsch provided an update via telephone and stated that the study would go live on December 15, 2015. She provided a timetable which indicated that UCSD began a pre-kiosk 6-month data collection during the last quarter of 2015. They will implement the device, enroll patients and refine data collection tools and processes during the first quarter of 2016, collect and review the data during the third quarter of 2016, and report back to the board with their results during the last quarter of 2016.

Sharp will be marketing the kiosk to its employees and encouraging them to use it.

Updates on this study will be provided at each quarterly Enforcement and Compounding Committee meeting while the study is underway.

Steve Gray, representing Kaiser, asked if the data would be comparable given the study design and the seasonal timeframe for the data collection. He also asked whether UCSD would report at a drug-specific level and whether the study would be able to compensate for seasonal fluctuations (e.g., cold/flu season). Dr. Hirsch answered that the study will look at the return to stock rate for the pharmacy vs. the kiosk.

Dr. Gutierrez asked whether the drug class would be included in the data. Dr. Hirsch stated she thought they should have thought about collecting data at the drug class level and would be open to adding that data.

Committee Recommendation:

Motion: Request the collection of drug classifications as part of the study.

M/S: Lippe/Hackworth

Support: 4 Oppose: 0 Abstain: 0

d. Sunset Review Proposals

The board's 2016 Sunset Report was submitted to the Legislature when it was due on December 1, 2015. Below are several issues highlighted in the report.

1. Regulation of Outsourcing Facilities by the Board

Background

In 2012, medication contaminated by fungal material that was compounded by a Massachusetts pharmacy killed 65 and injured approximately 700 individuals in various

states. In response, the California Board of Pharmacy initiated a review of its then sterile injectable compounding requirements that had been enacted in 2001. Among other actions, the board sponsored legislation in 2013 to increase licensure requirements for sterile compounding pharmacies (SB 294, Chapter 565, Emmerson). The legislation expanded the definition of sterile compounding to include injectable medications, inhalation products and medication applied in the eyes. The law also eliminated accreditation by outside agencies as an alternative to licensure with annual board inspections, and the board began a massive upgrading of its sterile compounding regulations, a process that is nearing completion in late 2015.

The November 2013 enactment of the federal Drug Quality and Security Act (DQSA) responded to the 2012 compounding tragedy in a new way: this legislation created a new type of entity authorized to compound medications – the outsourcing facility. These generally large-scale production facilities are authorized to compound large quantities of medications for use by other entities, whereas a pharmacy generally compounds pursuant to a patient-specific prescription. Medications prepared by outsourcing facilities must be done under current good manufacturing practices (or cGMPs), which are more stringent than compounding requirements for sterile compounding pharmacies, since many patients in multiple locations can receive these medications that are not usually linked to patient-specific prescriptions.

Currently California is licensing as sterile compounding pharmacies federally licensed outsourcing facilities located within or shipping medication into California. This is increasingly losing its viability as a regulatory solution. First, it does not recognize the federal outsourcing requirements that permit large scale compounding. Second multiple states are moving to establish regulatory frameworks to license outsourcing facilities as separate entities, and some bar licensure of these facilities in their home states as sterile compounding pharmacies. This is currently an issue in Mississippi, and will be an issue in July in New Jersey. Several other states have pending legislation in this area as well.

In 2015, the board sponsored legislation (SB 619, Morrell) to license outsourcing facilities as separate entities both within and outside California to ship into the state. This bill was held in suspense by the Senate Appropriations Committee. In 2016, the board seeks to resume pursuing regulation of outsourcing facilities as separate entities. The Senate Business and Professions Committee will evaluate outsourcing facilities as part of its evaluation of the impact of the DQSA during our sunset review. A legislative solution is likely to come as part of this review.

Discussion and Comment

At this meeting, Ms. Herold explained that the sunset review committee staff has indicated that establishing a licensing program for outsourcing facilities located within and outside California will be a sunset issue for the board to address. Ms. Herold foresees the board working with the committee staff to find a solution.

Steve Gray, representing Kaiser Permanente, suggested that any proposed legislation be specific when defining the provisions for a pharmacy and an outsourcing facility to do business at the same location.

Ms. Herold clarified that the board does not allow two licenses to share the same premises. Some rare exceptions include a 3PL and a wholesaler as well as a wholesaler and a veterinary retailer. Two different licensees need to have a hard wall between them, must have separate ingress and egress, and must maintain separate records.

2. Registration of Automated Delivery Devices in Use

Background

Pharmacies are able to operate automated dispensing machines or devices in various settings away from the licensed pharmacy. This includes in:

- Skilled nursing homes and other health care facilities licensed under Health and Safety Code section 1250 (c), (d) or (k) (the devices are authorized under section 1261.6 of the Health and Safety Code, authority for pharmacies to do this in specific locations is specified in Business and Professions Code section 4119.1)
- Clinics licensed under section 4180 of the Business and Professions Code (the devices are authorized under section 4186) – these include licensed, nonprofit community or free clinics defined under Health and Safety Code 1204(a)(1), a clinic operated by a federally recognized Indian tribe or tribal organization referred to in Health and Safety Code section 1206(b), a clinic operated by a primary care community or free clinic operated on a separate premises from a licensed clinic and that is open no more than 20 hours per week as referred to in Health and Safety Code section 1206(h), a student health center clinic operated by a public institution of higher education such as college health center as referred to in Health and Safety Code section 1206(j).
- Hospitals may use Pyxis or Pyxis-type machines throughout a hospital to store medication under application of provisions in Title 22 that allow drugs to be stored in nursing stations. The Pyxis and like devices are considered secured storage units for drugs.

The board has no idea how many of these machines are in use, where they are in use, or which pharmacy is responsible for any machine.

The demand for additional use of devices is growing. As scheduled earlier at this meeting, a pilot study is underway that if proven valuable, would allow patients to pick up medication from machines not specifically located in a pharmacy.

At the September 9, 2015, Enforcement Committee meeting, staff suggested that a simple registration be established for pharmacies that operate each of these machines that identifies their locations, as a beneficial step in board oversight and enforcement. The list

could be updated as needed via form submission to the board by a pharmacy adding, moving or removing a machine. This registration could operate much like the off-site storage waivers for records waivers. Then at annual renewal of the pharmacy, the pharmacy would update or confirm the list of machines it operates and where each is located. Staff noted that a regulation or statutory amendment is likely needed to establish this requirement.

Discussion and Comment

At this meeting, Dr. Gutierrez provided an overview of the background and Ms. Herold indicated that this proposal was one of the board’s three recommendations in the sunset report.

There were no questions or comments.

e. Proposal for Routine Inspections of Pharmacies every Four Years

Background

The board’s charge to regulate the pharmacy profession necessitates routine inspections of licensed facilities to confirm adherence to or identify failures in adherence to the requirements of pharmacy law. Failure to perform such inspections means that the board’s enforcement program is reactive rather than proactive and relies solely on being advised of a potential violation of pharmacy law via a complaint or other information that would trigger an investigation.

For a number of years the board has wanted to inspect all facilities every three or four years. The board has been unable to complete these routine inspections of all facilities with any regularity, and in recent years has had to substantially reduce such inspections. While inspections are completed, inspections occur generally as part of the investigative process, prior to issuance or renewal of a sterile compounding license or as part of probation monitoring.

All Inspections FY11-12 thru FY14-15 by Visit Type

# of Inspections					
Inspection Type	FY11-12	FY12-13	FY13-14	FY14-15	Total
Routine	1730	1010	287	342	3369
Investigation	743	896	875	926	3440
Probation/PRP	258	228	139	227	852
Sterile Compounding	268	276	996	1067	2607
Other	34	39	32	26	131

Grand Total	3033	2449	2329	2588	10399
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Mandatory inspections on a routine but random basis would enable the board to perform compliance inspections to educate licensees about pharmacy law as well as identify problems early to prevent more serious consumer issues from developing. Like all inspections, such inspections would be unannounced.

Compliance inspections provide an opportunity for board staff to answer questions about pharmacy law and to complete follow up inspections of facilities previously issued either citations or letters of admonishment to confirm compliance.

Mandatory inspections once every four years would be an alternative to our current practice of conducting inspections principally to investigate problems (or inspect sterile compounders).

The board currently has 6,572 community pharmacies licensed in California. Some of these pharmacies have never been inspected by the board. The creation of a statutory mandate directing the board to perform inspections of all pharmacies every four years would require approximately 1650 routine inspections annually. Over the last two years, the board completed an average of 1,215 inspections annually (routine plus investigation inspections).

Discussion and Comment

At this meeting, Dr. Gutierrez provided an overview of the proposal. Ms. Herold advised that the board needs to commit to performing the proposed inspections. The inspections would allow the board inspectors to work proactively as a resource for pharmacies instead of initiating inspections reactively based on complaints.

Committee Recommendation:

Motion: Motion to create a statutory mandate to complete random, unannounced routine inspections of pharmacies once every four years.

Steve Gray, representing Kaiser Permanente, inquired whether the motion was intended to include all facilities the board licenses or just pharmacies. Second, he asked whether the motion was intended to include nonresident pharmacies.

Ms. Herold clarified that the motion was intended to include resident pharmacies and non-resident sterile facilities only. Ms. Herold stated that the National Association of Boards of Pharmacy is conducting inspections on nonresident pharmacies and that the board has staff in place to review the reports if the pharmacy is licensed in California. The board wants to complete the inspections without increasing the inspector staff or raising fees.

Committee Recommendation:

Amended Motion: Create a statutory mandate to complete random, unannounced routine inspections of resident pharmacies once every four years.

M/S: Lippe/Hackworth

Support: 4 Oppose: 0 Abstain: 0

f. Discussion on Items in the News:

1. “Preventing Diversion in the ED” from www.pppmag.com, November 2015

Background

An article was added to the agenda by Board President and Committee Chair Gutierrez. In the article, the author asserted that drug diversion by health care workers is quite common. The article reviewed the techniques health care workers use to divert drugs and suggested multifaceted approaches for preventing and identifying diversion.

This item was informational only. There were no questions or comments.

2. Settlement Agreement Between the Drug Enforcement Administration and Massachusetts General Hospital for Drug Diversion

Background

Earlier this fall, the U.S. Drug Enforcement Administration alleged that Massachusetts General Hospital failed to make and keep records required by the Controlled Substances Act, and failed to provide effective controls and procedures to guard against theft and loss of controlled substances from October 4, 2011 through April 1, 2015. On September 28, 2015, Massachusetts General Hospital agreed to pay a settlement amount of \$2,300,000.

This item was informational only. There were no questions or comments.

g. Review of Controlled Substances Losses Reported to the Board

Background

Board discussions in recent meetings have included drug thefts from automated drug dispensing machines. Board staff was recently asked to tabulate how many controlled substances losses have been reported to the board from automated dispensing machines.

While there is no category listed on the DEA 106 report to capture this specific type of data, board staff reviewed all loss reports since January 1, 2015 and identified the following losses that had been identified in automated dispensing machines. When reviewing the data keep in mind that:

1. The amount of controlled substances reported lost is usually lower than the actual amount of loss determined at the end of an investigation, and

2. Without a reporting category for this type of loss, some losses from automated dispensing machines could be reported under other categories.

Reports of Losses Related to Automatic Dispensing Machines (ADMs: Pyxis, Omnicell, Acudose, etc.) January 1, 2015 - November 30, 2015	Total # Reports	ADM Losses - Percent of Total Reports	Total Dosage Units Lost
180	2,267	8%	6,714

*total dosages (mLs converted into 5mL dosage units and added to solids)

Board of Pharmacy License Type for ADM Losses	# of Reports
Hospitals	177
Pharmacies	3
Total	180

Type of loss	# of Reports
Pilferage/Possible Pilferage or Not following proper procedures by nurse(s)	97
Unknown cause	78
Lost in transit to/from Automatic Dispensing Machine	2
Automatic Dispensing Machine error	1
Possible Pilferage by Pharmacy Technician	1
Possible Theft by patient	1
Total	180

The board will begin reporting all controlled substances losses reported to the board at each Enforcement and Compounding Committee Meeting.

Discussion and Comment

At this meeting, Dr. Gutierrez provided an overview and asked Ms. Sodergren to provide an analysis of the data. Ms. Sodergren explained that the Total Dosage Units Lost data was skewed by one large loss of over 4,600 units. If the one large loss is removed, the average loss is actually about 11 dosage units.

Regarding types of loss, Ms. Sodergren clarified that losses where the type of loss was unknown were very small. The highest loss was 25 dosage units, but the majority of losses were 5 dosage units or fewer. It doesn't appear that there are significant losses where pharmacies are unable to identify the cause.

Lynn Paulsen, speaking for herself, stated she believed there is an opportunity to improve controls with automated delivery devices. Currently, each facility decides how to best monitor the devices. She suggested that there be a "safe harbor" wherein a PIC would not be disciplined if they could prove they followed established guidelines/best practices for detecting drug diversion.

Dr. Gutierrez recommended that the board review the Mayo Clinic process for identifying potential diversion.

Bill Maguire, representing Omnicell, stated he believes establishing a best practices guideline for pharmacies, both manual and automated, would be a good idea.

Dr. Gutierrez asked why vendors do not do a better job of educating their customers about the systems and best practices. Mr. Maguire answered that some vendors provide education, but some customers might become overwhelmed. He indicated that canned reports are available, but staff has to review them and decide which best fit their needs.

Committee Recommendation:

Motion: Invite vendors to come to the next enforcement and compounding committee meeting to discuss reports/best practices for diversion detection.

M/S: Lippe/Hackworth

Support: 4 Oppose: 0 Abstain: 0

h. Update on the CURES 2.0 Prescription Monitoring Program

Background

The California Department of Justice is continuing to work on upgrading the CURES system. On June 30, the DOJ had a "soft launch" of CURES 2.0 as the new system is called. Since then the DOJ has been working to pilot test the new system and install upgrades that will permit conversion to the new, enhanced system.

At the September 9, 2015, Enforcement Committee Meeting, staff from the California Department of Justice provided an update on the transition to the new CURES 2.0 system and advised the committee that CURES 2.0 should be available to users by January 2016. It was stated that 18,487 pharmacists, less than 50 percent of California's licensed pharmacists, had registered for CURES 2.0.

Meanwhile, the board continues to register pharmacists at continuing education events it hosts.

Discussion and Comment

At this meeting, Ms. Herold, who sits on the DOJ/DCA Change Control Board for CURES, provided an update on CURES 2.0 program. Ms. Herold stated that pharmacies will have until July 2016 to update their browsers to meet DOJ's security standards. Users must upgrade to Internet Explorer 11.0 or greater, or the most recent versions of Firefox, Chrome, and Safari. The Department of Justice will support CURES 1.0 until July 2016, but may only support CURES 2.0 afterward.

Ms. Herold believes online user registration will be available in January 2016. She indicated that DOJ is preparing an updated press release that should be available within the next few weeks. Once DOJ releases their update, the board will issue a new subscriber alert. Dr. Gutierrez asked that the board also include an article about CURES 2.0 enrollment in the next *The Script* newsletter.

Steve Gray, representing Kaiser Permanente, inquired whether other boards have indicated how or if they are going to confirm their licensees are enrolled as required. Dr. Gray suggested that the board send out its press release to national associations as well as state associations to account for licensed pharmacists living in other states or countries.

Angie Manetti, representing the California Retailers Association, was encouraged to hear that the deadline has been extended to July 1, 2016 as many of her members were in the process of completing complicated and expensive updates to their entire computer systems.

i. Enforcement Options for Patient Consultation Violations

Background

Nearly 25 years ago, the Board of Pharmacy promulgated regulations to require pharmacists to consult with patients every time they receive a medication for the first time. The board included in the regulation additional occasions where a pharmacist must consult a patient – where the patient has questions or the pharmacist believes a medication warrants consultation.

Sometimes California's requirements are confused with national requirements enacted about the same time by CMS for Medicare patients in what was known as "OBRA 90." However, California's requirements were actually adopted before OBRA 90's requirements. The OBRA 90 requirements provided that Medicare patients be offered consultation when they receive medication for the first time. So California's requirements, requiring the pharmacist to initiate consultation, were stronger and broader than the OBRA 90 requirements in that they

pertained to all patients, not just those whose medications were paid for by Medicare, establishing one standard of care for all patients in California.

After approval of California's patient consultation requirements, the board also delayed implementation of patient consultation at the request of the profession because pharmacists stated they could not provide consultation without the aid of pharmacy technicians. So the approved patient-consultation regulation was delayed so that the board could secure statutory authority and then promulgate regulations to establish the licensure of pharmacy technicians to "free" the pharmacist to provide consultation.

California's requirement is for the pharmacist to consult the patient – not to offer to consult. When doing the consultation rulemaking, the board emphasized that consultation was to be initiated by the pharmacist, and that any denial of the consultation must be made directly to the pharmacist, other staff (e.g., pharmacy technicians or ancillary staff) were not to screen for consultation by asking if the patient wanted to speak to the pharmacist or had questions about the medication. Consultation was required whenever the patient or the patient's agent was present in the pharmacy to receive the consultation.

Over the years, the board has added other enhancements to help ensure patients receive meaningful consultation, including a "Notice to Consumers" poster that must be posted in a pharmacy that specifically states the pharmacist must consult with each patient about his or her new medication, and lists the 5 questions a patient should understand before taking a prescription medication.

More recently in promulgating the requirements for patient-centered labels, the board required that oral consultation services be available in 12 languages to aid limited-English speaking patients in better understanding how to take their prescription medication.

Over the years, the board has enforced its patient consultation requirements in various ways. Initially it was one of the first violations for which the board used its citation and fine authority. In recent years, the board has typically assessed fines of approximately \$1,000 when it observes failure to consult during an inspection. Where a medication error has occurred and consultation was not provided, the board generally issues a higher fine.

In 2011, board staff began working on a project with three California district attorneys' offices to aid in the board's enforcement of patient consultation. Using the state's unfair business practices statute in Business and Professions Code section 17200, the DAs' offices were able to assess higher fines for failure to consult. Additionally, the DAs' offices used undercover investigators to pass prescriptions, an action the board has not done.

The DAs' investigations have resulted in more substantial fines to three pharmacy chains where investigations have been completed – CVS (2013, \$658,500), Rite Aid (2014, \$498,250) and recently Walgreens (2015, \$502,000).

At the September 9, 2015, committee meeting, the committee heard questions and comments from the public regarding whether the board can prohibit the use of a system that requires a patient to accept or decline patient consultation in advance of payment. The committee requested that the Communication and Public Education committee focus on consumer education and why patient consultation is important.

Discussion and Comment

This item was added to the agenda in the event the committee wished to discuss sanctions for failure to consult, or to wait for the Communication and Public Education Committee to complete its work on reviewing consultation matters before discussing sanctions.

Dr. Gutierrez indicated that it was her understanding that this item would be deferred to the Communication and Public Education Committee for follow up.

Ms. Herold verified that the Communication and Public Education Committee was given general responsibility for uncovering the reasons why consultations aren't being performed. She believed it was appropriate to wait until the Communication and Public Education Committee finishes its work before the Enforcement and Compounding Committee proceeds any further.

j. Discussion and Update to the Board's Emergency Response Policy

Background

On September 15, 2015, the board held an Emergency Board Meeting in response to the wildfires in Lake and Napa counties. In light of the recent use of the policy it is being brought to the board for evaluation and assessment to determine if changes to the policy are necessary.

At the October 28-29, 2015 board meeting, this item was referred to the enforcement committee for discussion.

Discussion and Comment

At this meeting, Ms. Freedman provided some background and discussed some of the challenges of the current policy. The current policy suggests that a meeting wouldn't need to be held pursuant to the open meeting act. She advised amending the opening statement to specify that if the board is not able to establish a quorum, three members would be able to exercise the board's authority pursuant to Business and Professions Code section 4062.

Ms. Freedman also stated that the board has other options including delegating the authority to a specific board member, perhaps the board president. She recommended that if the board chose that option, that it limit the authority to 14-30 days.

Committee Recommendation:

Motion: Modify board policy to delegate its authority pursuant to Business and Professions Code section 4062 to the board president for a period of 30 days.

M/S: Lippe/Hackworth

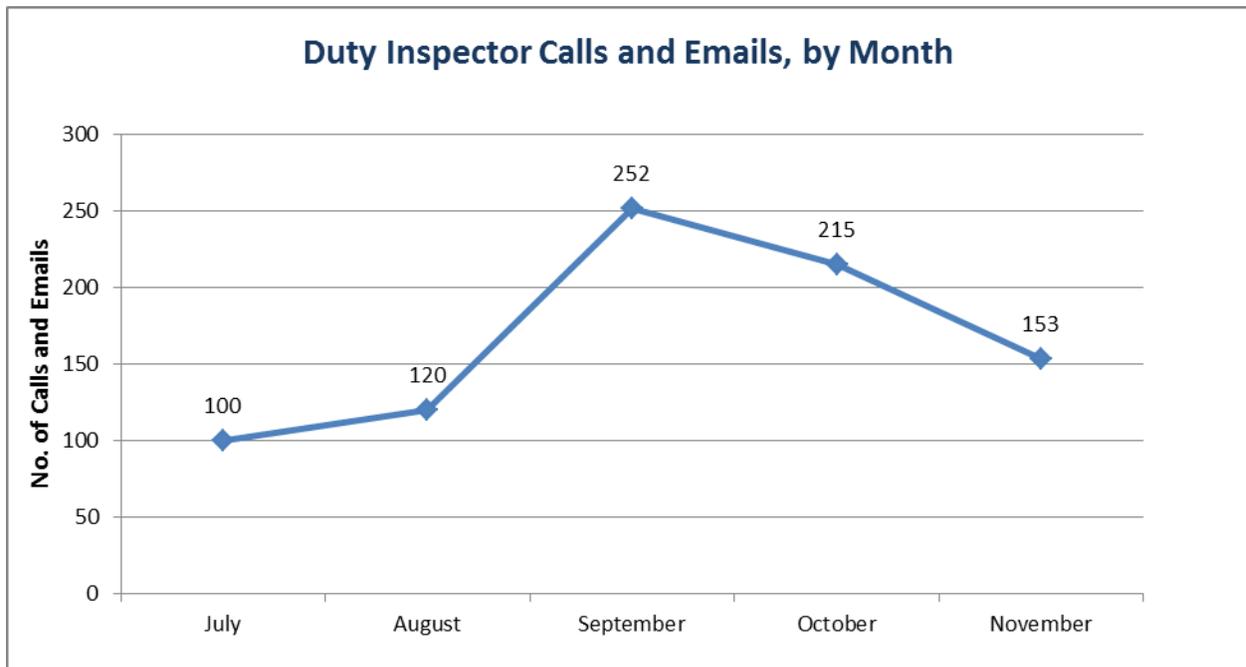
Support: 4 Oppose: 0 Abstain: 0

k. Review of Duty Inspector Activities

Background

Since July 1, 2015, Pharmacy Board inspectors have responded to 840 calls, an average of 168 calls each month. The board’s highest month was September, with 252 calls. July was the lowest month, with 100 calls.

Chart: All Inspector Calls, Trends by Month



In September, the board expanded its inspector answer program in two ways. First, the board tripled the hours inspectors take phone calls from six hours each week to 16 hours. Second, the board added the “Ask.Inspector” email box. Board inspectors respond to emails five days a week. Additionally, in September, licensees were sent a Subscriber Alert to let them know of the board’s expanded inspector hours.

The addition of the added call hours and the email box has resulted in a significant increase in activity. In September, inspector requests more than doubled from August. There were 120

calls in August and 252 in September, an increase of 115 percent. In September and October, inspectors handled more than 200 calls each month. In October and November, the number of calls declined but not yet back to the August levels.

The September spike in inspector calls may be temporary, but it is too soon to be certain. The board's office was closed for three days in November for holiday observances. It is possible these closures contributed to the declines.

We will continue to provide these statistics at future meetings.

The board's new public information officer is beginning to work to establish an online resource directory FAQ. The goal is to put many questions and answers online so individuals may find their own answers. The public information officer is just beginning training to do this.

Discussion and Comment

Dr. Gutierrez reviewed duty inspector activity statistics.

Ms. Herold indicated that the new Public Information Officer is working on an online FAQ directory. She estimated the FAQ's would be available in 30-90 days.

There were no questions or comments.

III. COMPOUNDING MATTERS

a. 2015 FDA Intergovernmental Meeting on Drug Compounding and Drug Supply Chain Security Held in November 2015

Background

On November 16 and 17, the FDA convened the 2015 Intergovernmental Working Meeting on Drug Compounding and Supply Chain Security. This meeting had representatives from about 45 states and was intended to exchange information with states as the 2013 Drug Quality Security Act is being implemented.

Executive Officer Herold and a deputy director from the California Department of Public Health were California's attendees.

The purpose of the meeting was to update states on emerging FDA policy regarding sterile compounding, outsourcing facilities and supply chain security requirements (the latter are the provisions that preempted California's e-pedigree requirements).

Most of the meeting focused on compounding/outsourcing requirements, with the last quarter of the meeting focusing on the licensing requirements for wholesalers and third-party logistics providers. Executive Officer Herold provided presentations during both segments.

Below is an overview of the agenda:

1. Compounding Regulatory Policy Update
2. Draft Standard Memorandum of Understanding between FDA and the States
3. Information Sharing and Disclosures (between state agencies and FDA)
4. A Comparison of US Pharmacopeial Convention General Chapter 797 to the Current Good Manufacturing Practice Regulations Enforced by DEA
5. Inspections of Sterile compounding Facilities and Enforcement
6. State Handling of Outsourcing Facilities
7. Overview of DSCSA Implementation
8. Wholesaler Distributor and 3PL Provider Licensing
9. FDA and State Collaboration

Discussion and Comment

At this meeting, Ms. Herold discussed and highlighted information from the FDA meeting. Specifically, Ms. Herold indicated that the FDA is inspecting pharmacies and notifying the state boards of pharmacy when follow-up is needed. Additionally, Ms. Herold stated that some states are inspecting outsourcing facilities using USP 797 (including California) although the FDA is regulating outsourcing facilities using Current Good Manufacturing Practices (CGMPs). The board has a bill that will become a sunset issue regarding the future regulation of outsourcing facilities.

Ms. Herold noted that many states are attempting to catch up to the new federal requirements and many don't have requirements to fingerprint their applicants. This highlights this disparity in regulation and oversight when shipping across state lines.

The FDA was to have some documents on wholesaler and 3PL licensure available on November 27, 2015, but the documents are still in the draft and review phase and are not yet ready for release.

Dr. Gutierrez asked for clarification on USP 797. Ms. Herold stated that 797 is a guideline that the FDA allows to be enforceable. Years ago, the board asked if the state could require 797 by itself, but the board's attorneys determined that the germane parts of 797 would have to be placed into law. The board is almost finished adding those germane parts of 797 to state law.

There were no public comments.

b. Development of a Waiver Process from Building Standards Requirements Contained in Proposed Title 16 California Code of Regulations Sections 1751 et seq.

Background

During the October 2015 board meeting, the board discussed and took action on proposed changes to compounding requirements. As part of this discussion, the board discussed the need to establish a waiver requirement for some of the structural requirements. Suggested components to facilitate such a process were included in the most recent modifications to the proposed regulation (where the comment period ended December 5). As proposed in the regulation (as subdivision 1735.6(f) and in 1751.4(l)), the waiver request shall:

1. be made in writing
2. identify the provision(s) requiring physical construction, alteration, or improvement
3. contain a timeline for any such change

Consistent with the proposed language which was noticed for comment, board staff will work on development of a specific format upon adoption of the language by the board. Board review of the last proposed modifications to the compounding regulation will be scheduled for the next board meeting.

This item was informational only. There were no questions or comments.

c. Review of “USP <800>: Key Considerations and Changes for Health Systems,” Hospital Pharmacy 2015; 501(1):941-949

Background

This topic was added to the agenda by President Gutierrez.

On March 28, 2014, the United States Pharmacopeia and the National Formulary (USP-NF) published USP General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings, as open for public comment in the USP Pharmacopeial Forum (PF) 40(3). USP <800> serves as a new standard to guide the handling of hazardous drugs in order to protect patients, health care personnel, and the environment. USP <800> describes hazardous drug handling related to the receipt, storage, compounding, dispensing, and administration and disposal of both sterile and nonsterile products and preparations. According to this review, “Although complying with USP <800> may seem to be a daunting task, it can be manageable if approached in a systematic organized way. “

The final version of the chapter will be published on Feb 1, 2016 and USP states it will become enforceable on July 1, 2018.

This item was informational only. There were no questions or comments.

IV. MEETING DATES FOR 2016

The Enforcement Committee will meet on the following dates during 2016:

- March 2, 2016
- June 1, 2016
- August 31, 2016

Dr. Gutierrez adjourned the meeting at 12:53 p.m.