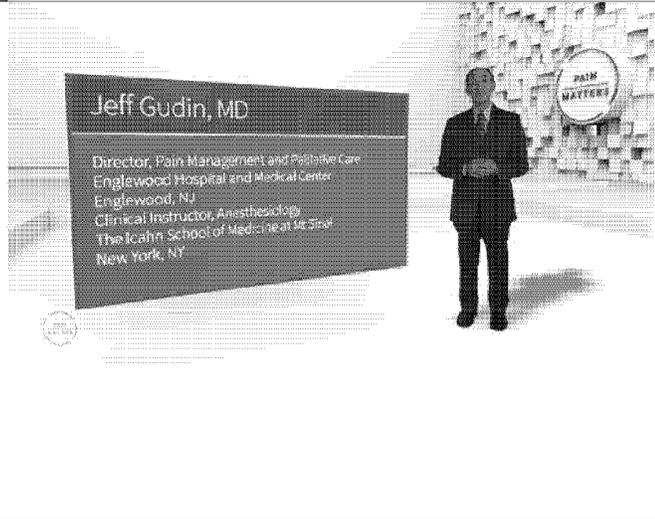
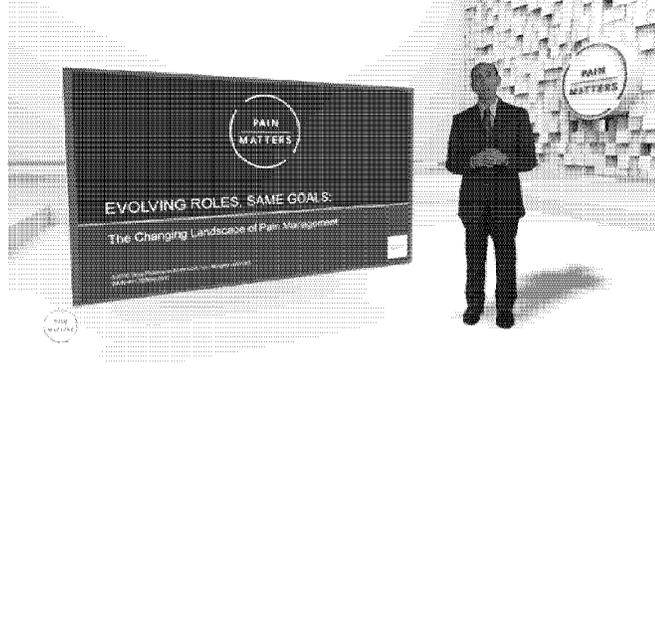
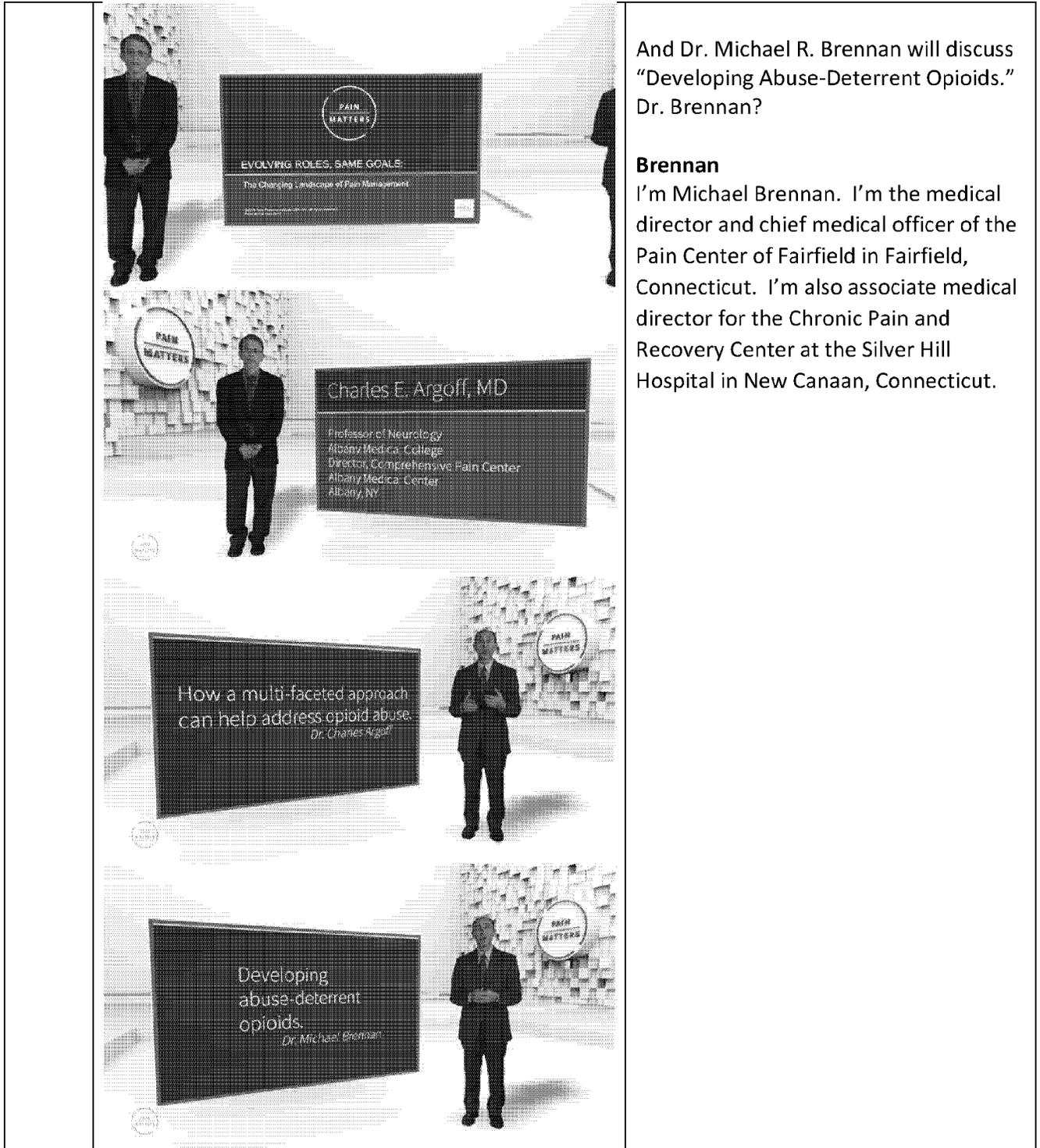


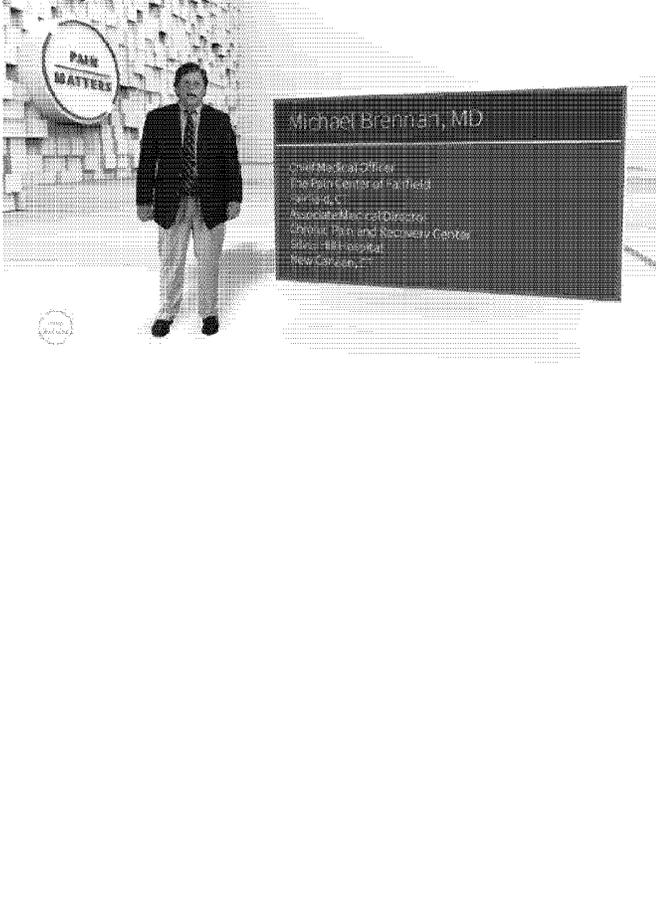
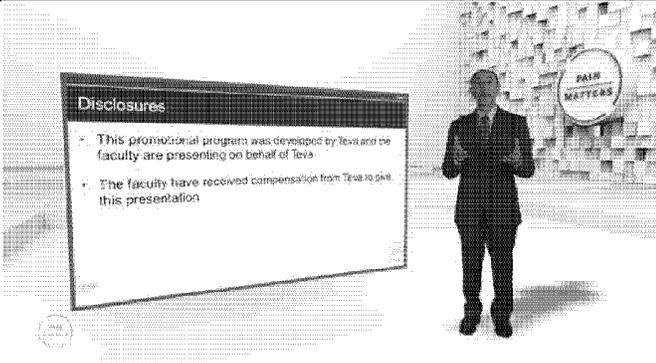
Part 1 – Program Introduction and Overview		
Slide #	Slide Image	Narration
N/A		<p>Introduction Music</p>
1		<p>Gudin</p> <p>Hello, my name is Dr. Jeff Gudín. I'm the director of pain management and palliative care at the Englewood Hospital and Medical Center in Englewood, New Jersey, and also a clinical instructor of anesthesiology at the Icahn School of Medicine at Mount Sinai.</p> <p>I want to welcome you to our program, entitled "Evolving Roles, Same Goals: The Changing Landscape of Pain Management."</p>
2		<p>Gudin</p> <p>Before we get started I'd like to take this opportunity to have our faculty introduce themselves. Dr. Argoff, why don't you start us off?</p> <p>Argoff</p> <p>I'm Charles Argoff, a professor of neurology at Albany Medical College and director of the Comprehensive Pain Center at Albany Medical Center in Albany, New York.</p> <p>Gudin</p> <p>Dr. Argoff will present "How A Multifaceted Approach Can Help Address Opioid Abuse."</p>



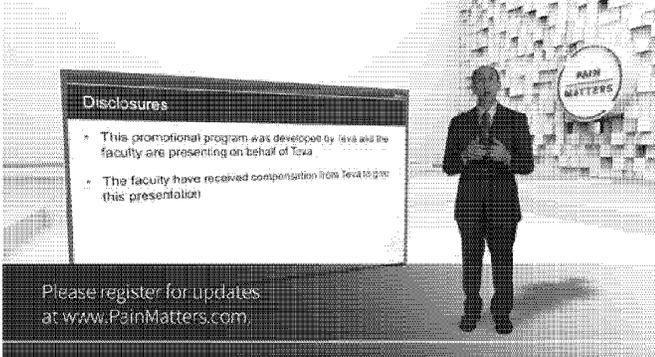
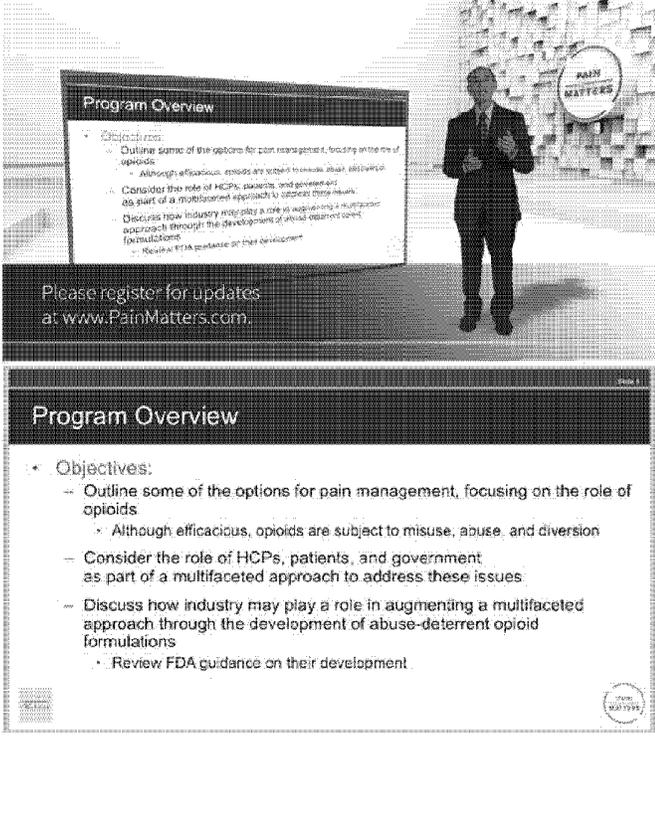
And Dr. Michael R. Brennan will discuss “Developing Abuse-Deterrent Opioids.” Dr. Brennan?

Brennan

I’m Michael Brennan. I’m the medical director and chief medical officer of the Pain Center of Fairfield in Fairfield, Connecticut. I’m also associate medical director for the Chronic Pain and Recovery Center at the Silver Hill Hospital in New Canaan, Connecticut.

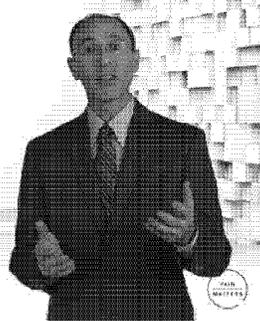
	 A man in a suit, Michael Brennan, MD, stands next to a large presentation board. The board displays his name and title: "Michael Brennan, MD", "Chief Medical Officer", "The Pain Center of Fairfield Hospital, CT", "Associate Medical Director", "Opioid Pain and Recovery Center", "Stamford Hospital", "New Canaan, CT". To the left of the board is a circular logo with the text "PAIN MATTERS".	
3	 A man in a suit, Michael Brennan, MD, stands next to a large presentation board. The board displays the word "Disclosures" and two bullet points: "This promotional program was developed by Teva and the faculty are presenting on behalf of Teva." and "The faculty have received compensation from Teva to give this presentation." To the right of the board is a circular logo with the text "PAIN MATTERS".	<p>Gudin</p> <p>I also want to let you, our audience, know that this program was developed by Teva Pharmaceuticals, that the three of us are presenting on behalf of Teva, and that we've been compensated by Teva to give this presentation.</p>

Pain Matters: Evolving Roles, Same Goals Video Script

	 <p>Please register for updates at www.PainMatters.com.</p>	
4	 <p>Please register for updates at www.PainMatters.com.</p> <p>Program Overview</p> <ul style="list-style-type: none">• Objectives:<ul style="list-style-type: none">– Outline some of the options for pain management, focusing on the role of opioids<ul style="list-style-type: none">• Although efficacious, opioids are subject to misuse, abuse, and diversion– Consider the role of HCPs, patients, and government as part of a multifaceted approach to address these issues– Discuss how industry may play a role in augmenting a multifaceted approach through the development of abuse-deterrent opioid formulations<ul style="list-style-type: none">• Review FDA guidance on their development	<p>Gudin</p> <p>Over the course of this program, we will discuss some of the issues we all deal with on a day-to-day basis when managing pain. Specifically, we'll take a look at treatment options, focusing on opioids. As we all know, opioids are used to treat pain but abuse can occur. As such, it's important that we, as clinicians, understand when and how to use them.</p> <p>We will also examine a multifaceted approach to addressing issues associated with opioids, and how healthcare professionals, patients, and the government can also play a role.</p> <p>Finally, we'll take a look at how the development of abuse deterrent opioids may play a role in this multifaceted methodology, taking information from the 2015 FDA Guidance on this topic.</p>

Part 2 – Complexities in Pain Management

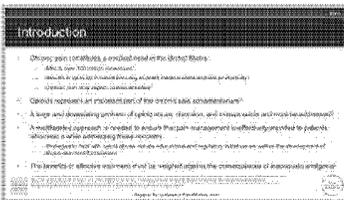
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Gudin

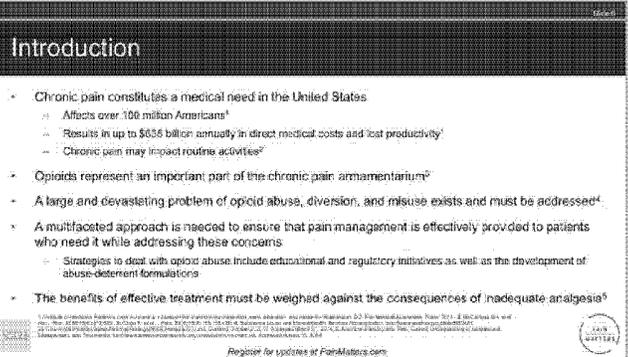
I would like to begin this program by talking about some of those day-to-day challenges a practitioner may face when it comes to pain management.

6



Gudin

Chronic pain constitutes a significant medical need in the United States. We recognize that patients are living longer with chronic illnesses, surviving their trauma or cancer, and as a result, may also be experiencing chronic pain.



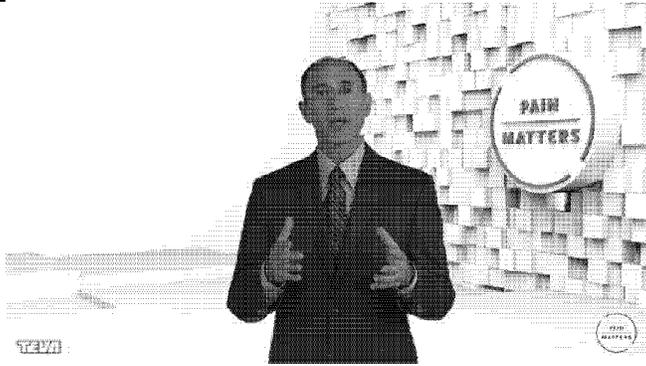
We know that chronic pain affects over 100 million Americans and costs this country a significant amount of money, estimated at over 600 billion dollars annually in direct costs and lost productivity. And we know that there's a cost to patients as well, that chronic pain may impair routine activities.

7



Gudin

Now, we know there are a few choices for analgesic medications, and opioid analgesics represent an important tool in our treatment arsenal. Unfortunately, with the expanding use of opioid analgesics, an epidemic of prescription opioid abuse has resulted.



One of the challenges for those of us who treat pain patients has been how to utilize these important analgesics safely and effectively. And what we've recognized is that there's no simple solution. A multifaceted approach is needed to make sure that pain management is adequately provided to patients who need it, while we also deal with the issues such as abuse, misuse, and diversion of these substances.

We have developed strategies to deal with opioid abuse, most notably focused around educating the many parties involved. The pharmaceutical industry has also stepped up and is trying to play a role in preventing the misuse and abuse of prescription analgesic medications. One way that they've done this is through the development of abuse-deterrent formulations for opioids. And any time we treat pain patients, as clinicians, we need to recognize the balance in our treatments. So we have to provide patients with adequate analgesia, but minimize the adverse events associated with those medications, and not just the physiological adverse effects, but also the adverse effects of opioid abuse, misuse, and/or diversion.

8

Opioids: An Important Analgesic Option

Opioid Prescriptions Dispensed by Retail Pharmacies—United States, 1991–2013

Year	Total Prescriptions (millions)
1991	76
1992	79
1993	82
1994	85
1995	87
1996	94
1997	97
1998	105
1999	110
2000	126
2001	138
2002	142
2003	149
2004	155
2005	159
2006	174
2007	184
2008	196
2009	202
2010	210
2011	219
2012	217
2013	207

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Gudin

I mentioned before that opioids are certainly an important analgesic option for pain management. This has been recognized over time. If you look at this chart, starting in the early 1990s, taking us up to 2013, you could see that there has been a slow, yet progressive increase in the amount of opioids dispensed by retail pharmacies in the United States. Again, this has to do with our improved abilities to assess pain and our willingness to treat chronic pain with a treatment regimen that includes opioids.

Unfortunately, the greater volume of opioid analgesics has also resulted in issues related to misuse, abuse, and diversion of these important analgesics.

9

Unintended Consequences of Abuse

Drug Overdose Deaths by Major Drug Type—United States, 1999–2010

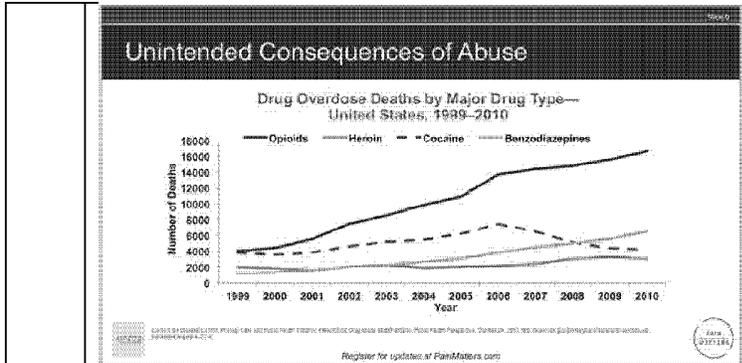
Year	Opioids	Heroin	Cocaine
1999	~1000	~500	~500
2000	~1100	~500	~500
2001	~1200	~500	~500
2002	~1300	~500	~500
2003	~1400	~500	~500
2004	~1500	~500	~500
2005	~1600	~500	~500
2006	~1700	~500	~500
2007	~1800	~500	~500
2008	~1900	~500	~500
2009	~2000	~500	~500
2010	~2100	~500	~500

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Gudin

Beyond increased misuse and diversion, there has also been an increase in deaths due to drug overdose. As you can see in this chart, prescription opioids outrank both heroin and cocaine combined as a cause of drug overdose deaths here in the United States.

Looking at the slope of these curves, you see that drug overdose deaths due to



prescription opioid use has outpaced heroin and cocaine over the last 10 years or so, highlighting the need to develop strategies to prevent prescription opioid misuse and abuse.

10

What Is the Scope of Intended Abuse/Addiction?

- Data derived from an evidence-based review of chronic pain patients with non-malignant pain receiving chronic opioid analgesic therapy
- 67 studies that evaluated
 - Abuse/addiction rate (24 studies, n=2307)
 - Absent drug-related behaviors (ADRBs) (17 studies, n=2466)
 - Urine test results (5 studies, n=1365)
- 25x lower rate of abuse/addiction in patients without a prior history (0.19% vs 5.0%)

3.27%
Percent of patients being treated with chronic opioid therapy with high likelihood of abuse/addiction

Gudin
David Fishbain, a psychiatrist and pain management specialist from the University of Miami, conducted an evidence-based review of the chronic pain literature, focusing on patients with non-cancer and non-malignant pain who were receiving chronic opioid analgesic therapy. He looked at 67 different studies that evaluated the abuse or addiction rate, aberrant drug-related behaviors, and urine toxicology testing.

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And what he found is that only 3.27 percent of patients being treated with chronic opioid therapy had a high likelihood of abuse or addiction with their opioid analgesics. Most notably, he found a 25 times lower rate of abuse or addiction in patients who didn't have a prior history of abuse or addiction.

This is an important data set for us to recognize that the risk is clearly greater in patients with a previous history of abuse or addiction and that it's relatively low for patients with chronic non-malignant pain who don't have a previous history

11

Source of Opioid Diversion with Increasing Nonmedical Use^{1,2}

- Although the most common initial source of opioids for nonmedical use is through friends and family,¹ the primary source changes with increased nonmedical use²

Most Common Source of Opioid by Frequency of Nonmedical Use

Number of Days of Nonmedical Use	Given by a friend or relative for free (%)	Prescribed by a physician (%)
1-29	61.9	17.9
30-59	48.3	19.5
100-199	37.7	33.5
200-365	26.4	27.2

1. 7th National Prescription Opioid Abuse Research Report (2014) by Lawrence A. Green, MD, MPH, and Robert A. Hays, MD, MPH. 2. Green et al., N Engl J Med 2014; 371:1097-1105. DOI: 10.1056/NEJMsa1408000. Copyright © 2014 Massachusetts Medical Society. Register for updates at PainMatters.com

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of addiction.

Gudin

We all know that the most common initial source of opioids for non-medical use comes from a friend or family member for free, but as the frequency of non-medical use increases, the opioid becomes more likely to come from a clinician, highlighting the need for us to educate and reinforce to our patients how to use their medication appropriately.

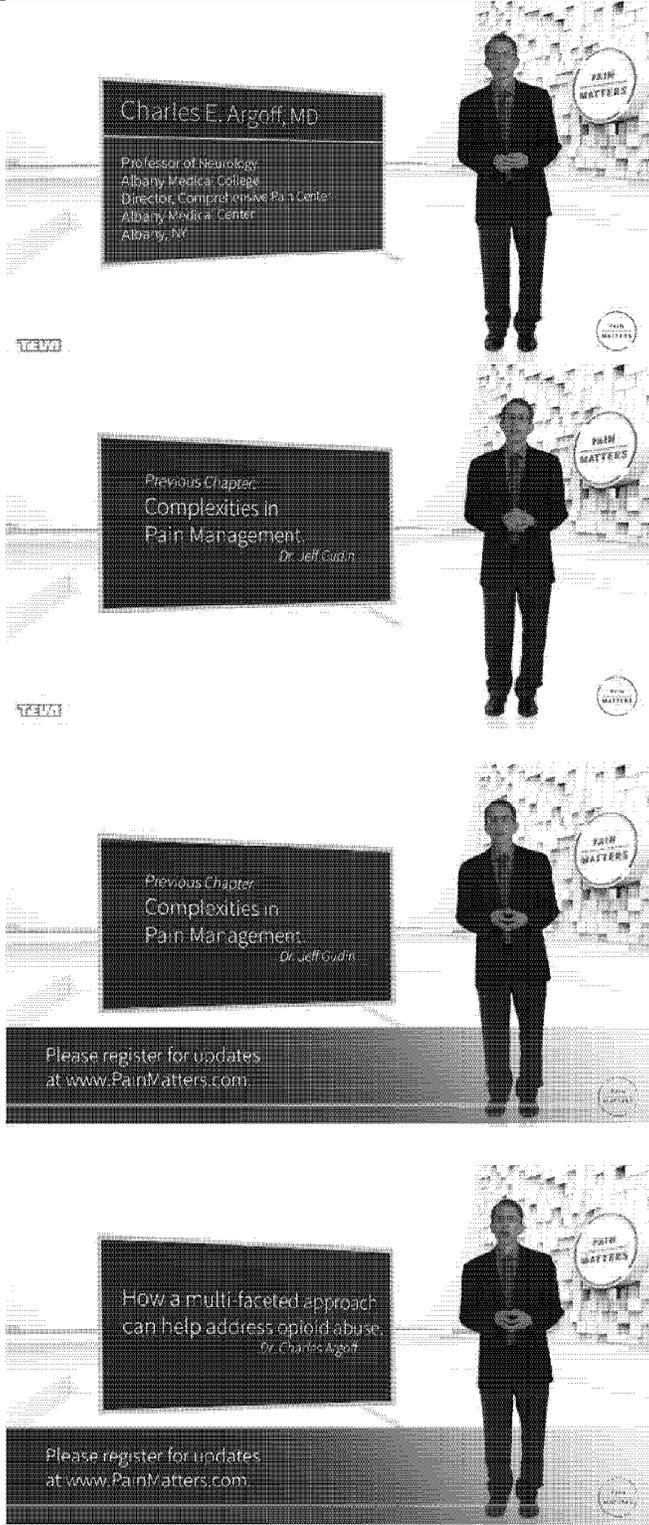
This brings us to the end of our discussion on some of the complexities clinicians face in pain management, and I hope you found this chapter informative.

Please return to the main menu and select the next chapter to hear Dr. Argoff tell you more about the role that clinicians and others can play in addressing opioid abuse.

	Video Image	Closing Music
		

Part 3 – Addressing Opioid Abuse: A Multi-Faceted Approach

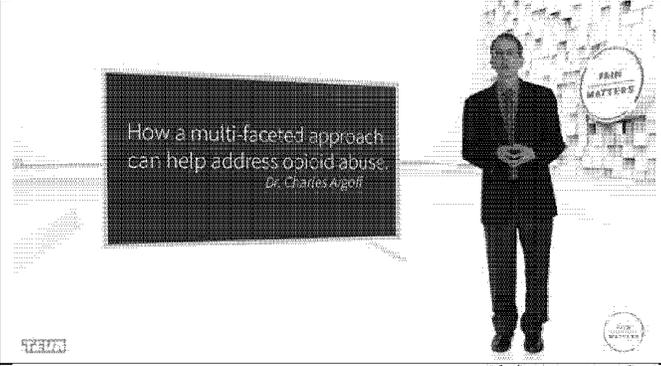
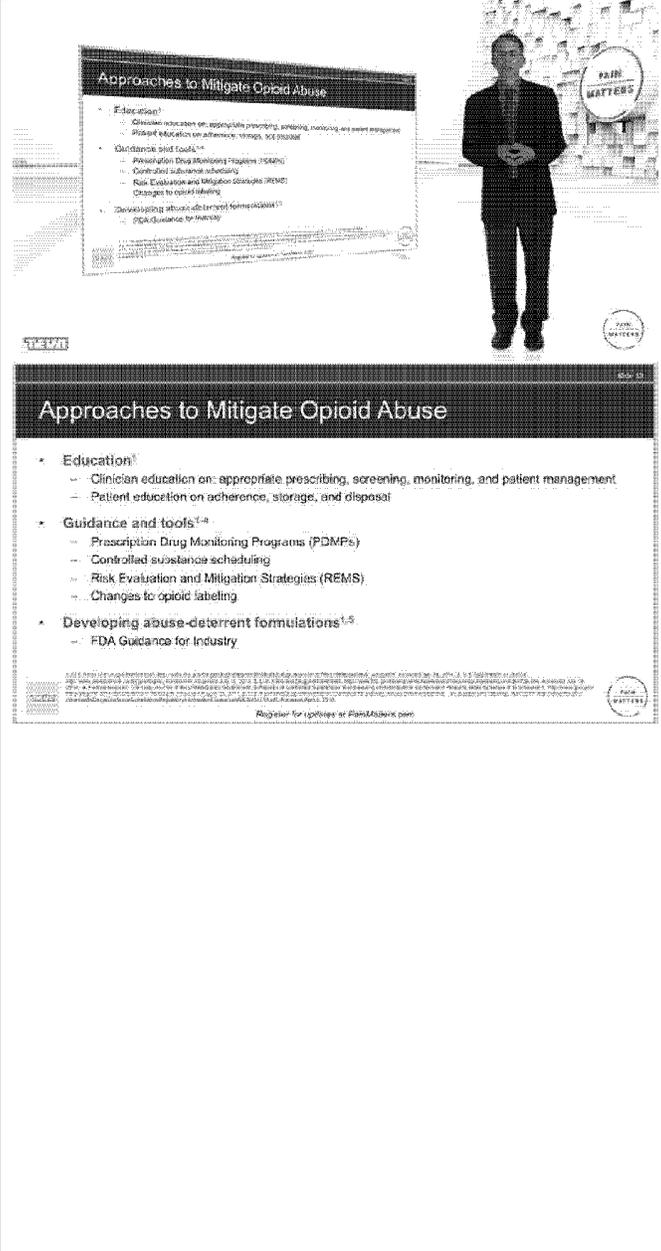
12



Argoff

I'm Charles Argoff, professor of neurology at Albany Medical College and director of the Comprehensive Pain Center at Albany Medical Center in Albany, New York.

In the previous chapter, you heard Dr. Jeff Gudim discuss some of the challenges we face with balancing the need for effective pain management with some of the dangers of prescription opioid use. To continue this conversation, I'll focus on how we can help address opioid abuse with a multifaceted approach.

		
<p>13</p>	 <p>Approaches to Mitigate Opioid Abuse</p> <ul style="list-style-type: none"> • Education¹ <ul style="list-style-type: none"> – Clinician education on: appropriate prescribing, screening, monitoring, and patient management – Patient education on adherence, storage, and disposal • Guidance and tools¹⁻⁴ <ul style="list-style-type: none"> – Prescription Drug Monitoring Programs (PDMPs) – Controlled substance scheduling – Risk Evaluation and Mitigation Strategies (REMS) – Changes to opioid labeling • Developing abuse-deterrent formulations^{1,5} <ul style="list-style-type: none"> – FDA Guidance for Industry <p><small>© 2015 Teva Pharmaceuticals USA, Inc. All rights reserved. Teva, the Teva logo, and Pain Matters are trademarks of Teva Pharmaceuticals USA, Inc. All other trademarks are the property of their respective owners. Register for updates at PainMatters.com</small></p>	<p>Argoff</p> <p>There are many approaches to mitigate opioid abuse, and I would like to divide them into three main buckets.</p> <p>First, it's education that ensures clinicians understand how to screen, monitor, and manage patients appropriately with opioid therapy. This can also be combined with patient education on adherence to a treatment regimen, as well as appropriate storage and disposal of opioids.</p> <p>Second is the availability and use of tools that can help us guide the approach to managing a person on opioid therapy. For example, prescription drug monitoring programs, which have been developed in almost every state, help us as clinicians see what controlled substances our patients are currently being prescribed. We have also had scheduling changes regarding certain opioids. We have risk evaluation and mitigation strategies, or REMS programs, to help us guard against opioid abuse, changes to opioid labeling, and guidance from the FDA on developing abuse-</p>

		<p>deterrent formulations.</p> <p>The FDA guidance outlines how abuse deterrent properties can be tested and what statements the FDA might allow in the product's package insert based on study results.</p>
<p>14</p>		<p>Argoff</p> <p>It's important to recognize that there are multiple stakeholders who are involved in addressing opioid abuse and it is necessary for there to be a collaborative approach among these groups.</p> <p>These groups include healthcare professionals who are currently involved in managing patient care, the patients themselves, State and Federal government entities, as well as industry. To promote safe and effective pain management, we can incorporate a multifaceted approach among all parties to recognize and mitigate the risks associated with opioid use.</p>
<p>15</p>		<p>Argoff</p> <p>Healthcare providers can play a role by following universal precautions, incorporating screening strategies, and monitoring patient adherence to prescription opioids.</p> <p>Some of the elements of universal precautions are outlined here, and include establishing a diagnosis, incorporating the use of a treatment agreement, periodic pain assessments, reviewing the diagnosis, and of course, ensuring appropriate documentation.</p>

HCP Approaches to Mitigate Opioid Abuse

How often are these done in "low-risk" patients?

Universal Precautions	Screening	Adherence Monitoring
<ul style="list-style-type: none">Establishing diagnosisTreatment agreementPain assessmentsReview of diagnosisDocumentation	<p>Various instruments including:</p> <ul style="list-style-type: none">Opioid Risk Tool (ORT)Current Opioid Abuse Measure (COAM)Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R)Pain Assessment & Documentation Tool (PADT)	<ul style="list-style-type: none">Prescription drug monitoring programs (PDMPs)Random drug screensPill counts

HCPs are at the forefront of pain management and employ multiple methods to assess opioid risk in individual patients.

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In terms of screening, there are various instruments that we can use as healthcare providers to identify the risk of opioid abuse in our patients, and some of them are listed here.

We also have adherence monitoring approaches. State-specific prescription drug monitoring programs provide us with some insight into the use of opioids by a particular patient, but these may vary widely between states.

Random drug screens are important. Random urine drug screens may be a way of confirming or evaluating adherence for the people to whom we prescribe medications, as is pill counting to see whether it appears that the person who we're prescribing the medication to is actually using it in a way that we have prescribed it and is adhering to that regimen. Keep in mind, even though we might consider any of our patients to be low risk for opioid abuse, no patient has zero risk. As healthcare providers, we are the front line against opioid abuse, and as such, we need to use multiple methods to support safe and effective use of the treatments we prescribe.

17

What is a PDMP?
Prescription Drug Monitoring Program:

- Definition**
 - Statewide electronic database
 - Collects data on substances dispensed in state
 - Housed by designated state agency (e.g. regulatory, administrative, law enforcement)
 - Accessible to authorized personnel
- Benefits**
 - Supports legitimate access to controlled substances
 - Identifies and deters drug abuse and diversion
 - Facilitates identification and treatment of those addicted to prescription drugs
 - Provides use and abuse data to inform public health efforts
 - Educates individuals on use, abuse, and diversion

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and if that’s not available, the Office of Drug Control national policy recommendations have been established and can be accessed to allow for an environmentally friendly disposal approach to these medications.

Argoff
 So what exactly is a prescription drug monitoring program, or PDMP, for short? By definition it is a statewide electronic database and it is designed to collect data on substances dispensed in that particular state. It is housed within a designated state agency, so it could be a regulatory, administrative or law enforcement agency; this may vary from state to state and it’s accessible only by authorized personnel.

What are the potential benefits? Well, this is a program that allows us to see what controlled substances a specific patient may be receiving in that state and in that way it helps to support legitimate access to controlled substances.

PDMPs may also be able to help identify and deter drug abuse and diversion. They may be able to facilitate identification and treatment of those addicted to prescription drugs by detecting certain patterns, which can be very helpful in cases where addiction is not obvious.

They also allow you to establish that you will be monitoring every

		<p>patient's opioid use patterns.</p> <p>They may provide use and abuse data to support public health efforts to help educate all of us, especially our patients, on how to effectively use medications and how we can all play a role in limiting abuse and hopefully reduce diversion.</p>
<p>18</p>		<p>Argoff</p> <p>As you see, Missouri is the only state currently without an enacted prescription drug monitoring program and most other states have an operational prescription drug monitoring program.</p> <p>PDMPs vary state by state, but in general they all are constructed to help clinicians understand how patients use prescription opioids, which may then impact our prescribing behavior. This can be used to help reduce doctor shopping and to promote greater transparency.</p> <p>It's also fair to say that the full benefit of prescription drug monitoring programs will not be reached until all states implement data sharing and interoperability between each other to ensure transparency of opioid use across state lines.</p>

19

Medicaid "Lock-In" Program
1 Patient, 1 PCP, 1 Pharmacy

- The Law**
 - Federal law allows Medicaid to restrict patients who overutilize Medicaid services to designated providers
- The Application**
 - High-risk opioid users can be restricted ("locked in") to receive treatment and prescriptions from a designated PCP and/or pharmacy
- The Purpose**
 - Single provider can coordinate care
 - Reduces doctor/pharmacy shopping
 - Limits drug diversion
 - Reduces healthcare utilization and pharmacy costs
- Future**
 - Lock-in programs might be adopted by other governmental payers and possibly private insurers as well

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Argoff

Those of you with patients on Medicaid may be aware of its lock-in program, which provides some ideas on how to limit abuse as well.

Federal law allows Medicaid to restrict patients who overutilize Medicaid services to designated providers. It does so by requiring a patient to be seen by one healthcare provider and obtain their prescriptions from a single pharmacy.

The purpose of this is to empower a single provider to coordinate care, to reduce doctor and pharmacy shopping, to limit drug diversion, and to reduce healthcare utilization and pharmacy cost. In the future, this model may be adopted by other governmental payers beyond Medicaid and even by private insurers as well to accomplish the same goals.

20

DEA Changes to Opioid Scheduling

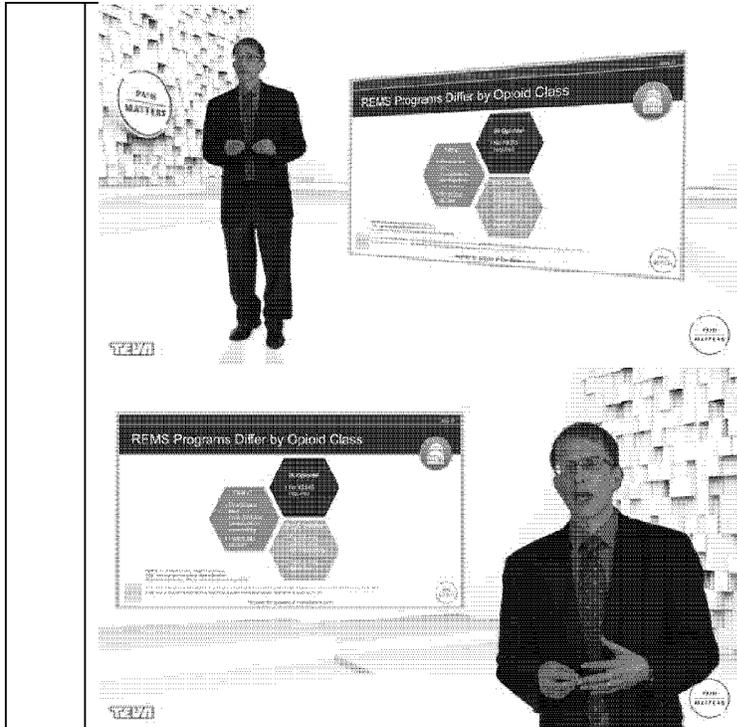
Schedule 3 → Schedule 2

Higher potential for abuse and dependence → Lower potential for abuse and dependence

Argoff

As we alluded to earlier, controlled substances scheduling of opioids can also help address prescription opioid abuse. As you know, the lower the number, the higher the potential for abuse and dependence.

Hydrocodone products were rescheduled from Schedule 3 to Schedule 2 in late 2014, which makes the process of obtaining a prescription and refills somewhat more difficult.

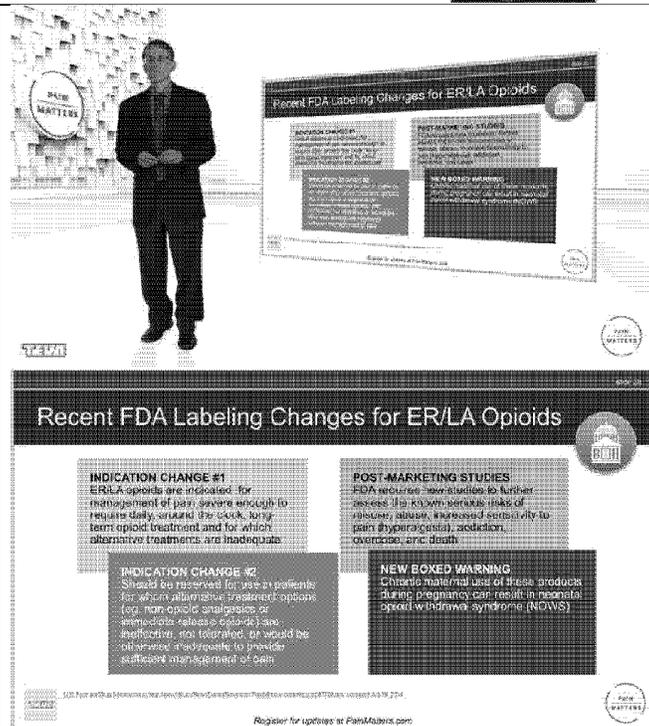


activities and have scored successfully on an examination.

In other words, not everyone with a DEA number can prescribe these medications. There has to be an additional set of educational activity before that can happen.

With extended-release and long-acting opioid therapy, participation in the REMS program is not mandatory for the practitioner and access is not restricted to prescribers who have fulfilled certain criteria.

23



Argoff

The federal government, through the FDA, can also change what's in the package insert of a product. Here, you see some changes in the package inserts of extended-release opioids that were implemented in 2013.

As you can see, the indication itself for extended-release and long-acting opioids has changed in two ways.

The first change specifies that extended release or long-acting opioids are indicated for management of pain severe enough to require daily around the clock, long-term opioid treatment and for which alternative treatments are inadequate.

		<p>The second change states that these agents should be reserved for use in patients for whom alternative treatment options (for example, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated or otherwise inadequate to provide sufficient management of pain.</p> <p>There are also postmarketing studies the FDA now requires. The FDA specifically is requiring new studies to further assess the known serious risks of misuse, abuse, and increased sensitivity to pain (sometimes known as hyperalgesia), addiction, overdose, and death.</p> <p>Finally, there is also a new boxed warning that states QUOTE chronic maternal use of these products during pregnancy can result in neonatal opioid withdrawal syndrome or NOWS. CLOSE QUOTE.</p>
<p>24</p>		<p>Argoff</p> <p>To summarize, we need to really consider a multifaceted approach to addressing opioid abuse. The key stakeholders in this multifaceted approach include healthcare providers, patients, government, as well as industry. As we discussed, healthcare provider strategies for mitigating opioid abuse include universal precautions, screening for drug abuse and abuse risk, urine testing, and adherence monitoring.</p>

A Multifaceted Approach to Addressing Opioid Abuse

- Key stakeholders in addressing opioid abuse include HCPs, patients, and government
- HCP strategies for mitigating opioid abuse include universal precautions, screening for drug abuse and abuse risk, urine testing, and adherence monitoring
- Patients should be educated on the methods and importance of safe use, safe storage, and safe disposal of opioids
- The federal and state governments have developed and are developing programs aimed at making opioid diversion and abuse more difficult and less likely, including:
 - PDMPs
 - REMS
 - Labeling changes
- Industry may also have a role by developing abuse-deterrent opioids

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Patients should also be educated, specifically on the methods and importance of safe use, safe storage, and safe disposal of opioids.

The Federal and State government have developed and continue to develop programs aimed at making opioid diversion and abuse more difficult and less likely including the use of prescription drug monitoring programs, the risk evaluation and mitigation strategy programs or REMS, and labeling changes.

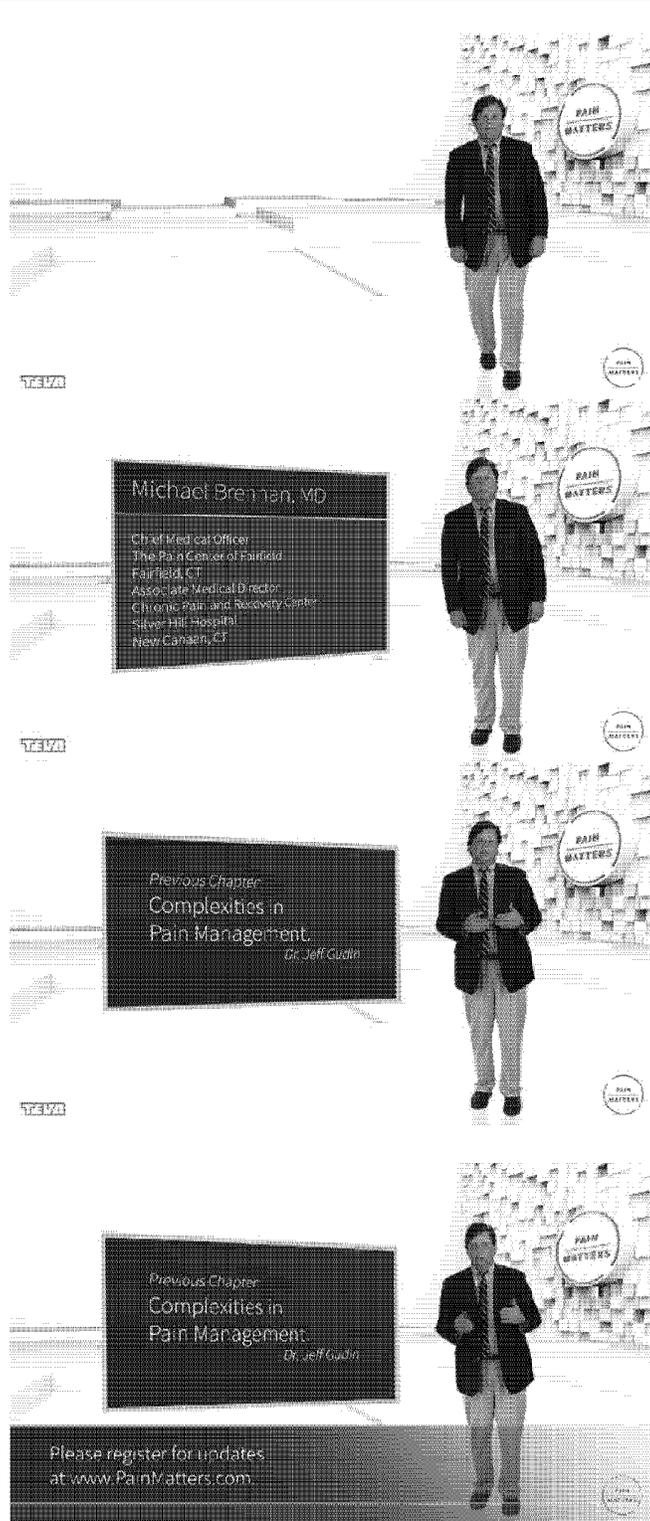
I hope you enjoyed this chapter of the program and better understand the role that healthcare providers, patients, and the government play in a multifaceted abuse mitigation strategy.

Industry may play a role in helping mitigate opioid abuse. To tell you a little more about this and the potential role of abuse deterrent opioids, please watch the final chapter in this series presented by Dr. Michael Brennan.

	Video Image	Closing Music
		

Part 4 – Developing Abuse-Deterrent Opioids

25



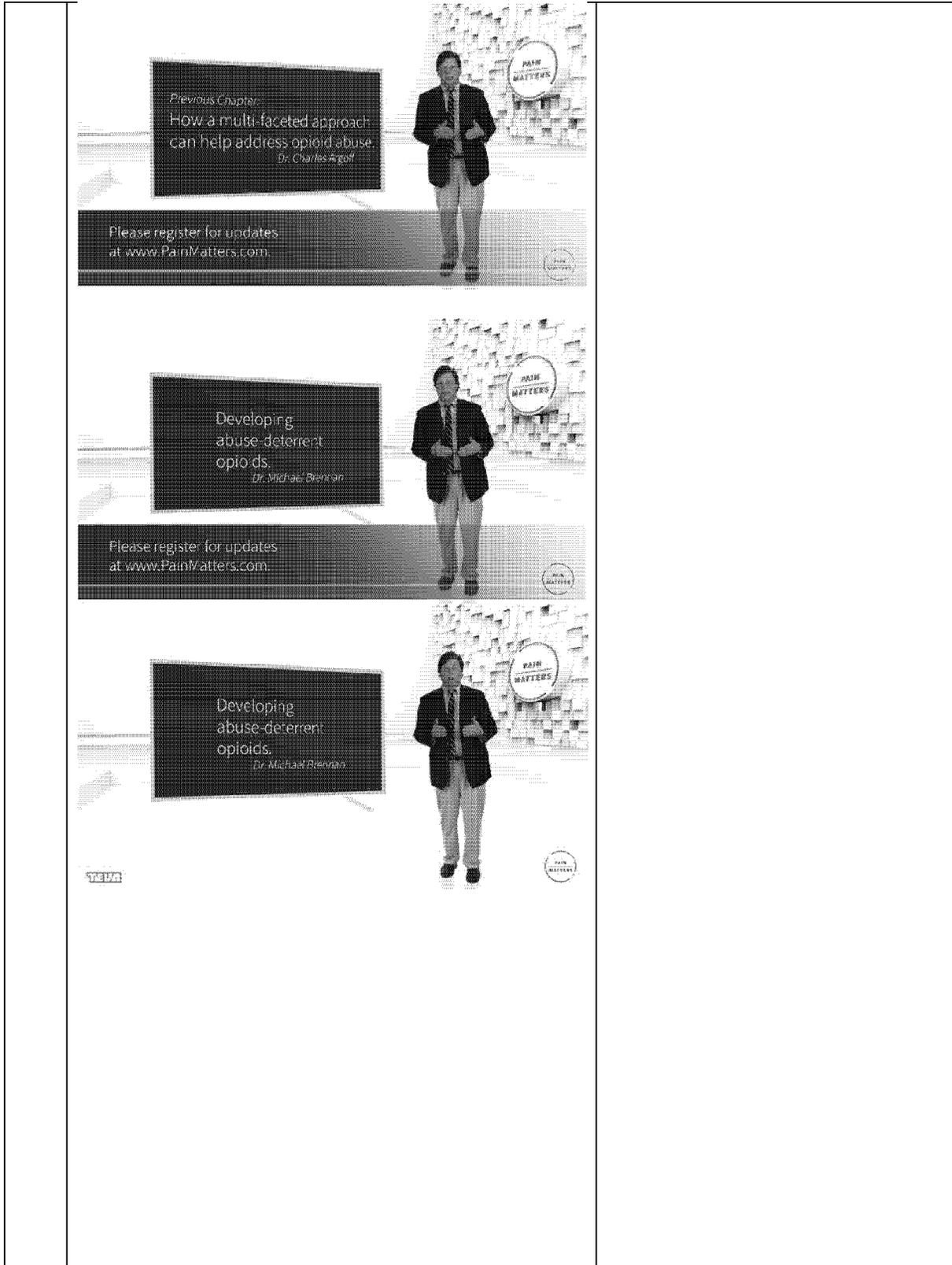
Brennan

I'm Michael Brennan and I'm the medical director and chief medical officer of the Pain Center of Fairfield in Fairfield, Connecticut.

I'm also associate medical director for the Chronic Pain and Recovery Center at the Silver Hill Hospital in New Canaan, Connecticut.

Over the previous chapters in this program, you heard about some of the issues associated with opioid use and how healthcare providers, patients, and the government can help reduce risks associated with opioid therapy.

Now, I'm gonna to tell you about the potential role that the pharmaceutical industry might play in mitigating opioid abuse, specifically through the development of abuse-deterrent opioids.



26

Various Approaches to Abuse-Deterrent Opioids

- 1. Physical/Chemical Barriers**
 - May prevent crushing, crushing, cutting, grating, or grinding
 - May resist extraction by solvents
- 2. Antagonist/Antagonist Combinations**
 - May cause euphoria when formulation compromised
 - Antagonist may be formulated to be selectively active only when tampered with
- 3. Aversion**
 - Substances may be added to create unpleasant effects when tampered with or taken at higher doses
- 4. Delivery System**
 - Drug release designs or method of drug delivery may offer resistance to abuse

Novel Approaches

- Use of technologies not captured by any of the above

Combination

- Use of two or more of the above

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Brennan

You'll see that there are 7 general approaches that have been recognized by the FDA as categories of abuse deterrent opioids. These include physical/chemical barriers, agonist/antagonist combinations, aversion substances added to the analgesic, delivery system characteristics, new molecular entities and pro-drugs, combination approaches, and novel approaches.

Regardless of the different approaches to these formulations, keep in mind that all of these products share one important commonality: when the medication is taken as directed or intended, the opioid works like a medication that does not include abuse deterrent properties. It's only when the formulation is tampered with that the abuse-deterrent properties become evident.

So that's the technical issue, right? Creating a drug that will work for pain, but at the same time making it difficult for somebody to want to abuse that drug or make abusing the drug less beneficial.

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FDA Guidance for Industry

Abuse-Deterrent Opioids – Evaluation and Labeling

Provides recommendations on:

- Studies that should be conducted to demonstrate that a formulation has abuse-deterrent properties
- How those studies will be evaluated

Also discusses implications in product labeling

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So where does the industry get their guidance? There was a guiding principle document that was published by the FDA in April 2015.

I'm going to provide you with an overview of what's contained within the guidance for developing abuse-deterrent opioid formulations.

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FDA Guidance for Industry (cont'd)

FDA guidance document on Abuse-Deterrent Opioids

- Categories of studies that address abuse-deterrent properties
- Description of studies of such studies
- Examples of labeling requirements, trial design, or program impact on the results of these studies

Categories of Studies:

1. Studies that demonstrate that a formulation has abuse-deterrent properties
2. Studies that demonstrate that a formulation has abuse-deterrent properties
3. Studies that demonstrate that a formulation has abuse-deterrent properties
4. Studies that demonstrate that a formulation has abuse-deterrent properties

Brennan

There are four study categories that can be used to assess the potential abuse-deterrent properties of an opioid.

And as we get into the types of abuse deterrent technologies, it'll become clear that certain technologies may meet one type of study and prove beneficial, but not necessarily a different type.

The first group of studies are

FDA Guidance for Industry (cont'd)

FDA guidance document outlines:

- Categories of studies to evaluate abuse-deterrent properties
- Designs and goals of such studies
- Examples of labeling statements that could be proposed based on the results of these studies

Categories of Studies

1	1 Abuse-Deterrent Formulation (ADF) Studies Evaluate the ability of the formulation to resist tampering and/or extraction studies.	3	3 Control Abuse Potential (CAP) Studies Evaluate the potential for abuse of the drug in its unaltered and altered states.
2	2 Pharmacokinetic Studies Evaluate the PK profiles of tampered and intact drug formulations.	4	4 Pharmacokinetic Studies Evaluate the PK profiles of tampered and intact drug formulations.

* Also with human abuse data for OTC products.
All new oral formulations of drugs for pain, muscle relaxants, sedatives, and sleep aids, etc. are required to undergo tamper-resistant testing.
Visit www.fda.gov/oc/ohrt/ohrt.html

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The man is speaking and gesturing with his hands. The screen behind him shows the same FDA guidance document as in the previous block.

FDA Guidance for Industry (cont'd)

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laboratory manipulation and extraction studies. These determine if tampering with the drug can override the formulation and provide access to the unadulterated opioid.

The next are pharmacokinetic studies. These studies look at how the abuse-deterrent properties exert an effect on the pharmacokinetic profile of the drug, and after the drug has been manipulated in the lab, if there's an alteration in the pharmacokinetic profile.

Examples of such alterations may include changes in bioavailability of the drug or changes to peak plasma concentration.

The third type of test is the clinical abuse potential study. These are studies that look to see how attractive or liked by recreational drug users the drug is in its unaltered and altered states.

Finally, and perhaps the greatest hurdle, will be the postmarket studies. Has there been a demonstrable reduction in abuse based upon the availability of a certain drug in the market? As you can imagine, it's going to take several years to determine if there's been an effect.

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Examples of Labeling Statements

Categories

1 These *in vitro* data demonstrate that Tramadol has physical and chemical properties that are expected to differ oral, nasal and intravenous abuse. However, abuse of this product is still possible by the *abst* route.

1&2 These *in vitro* data demonstrate that Tramadol has physical and chemical properties that are expected to differ oral, nasal and intravenous abuse. However, abuse of this product is still possible by the *abst* route.

2&3 These data alongside the results from clinical abuse-specific studies indicate that Tramadol has properties that are expected to differ abuse in the oral, intravenous, and intranasal routes. However, abuse of Tramadol by these routes is still possible.

1-4 These data demonstrate a restriction in the abuse of Tramadol in the community setting compared to the levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterrent properties were available. This restriction in abuse appears to be attributable to the product's formulation. However, such abuse of this product is still possible.

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Now, there are different categories of labeling statements that may be proposed for the package insert, and these depend on the results of studies conducted.

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FDA Guidance for Laboratory Manipulation and Extraction Studies

Study Design

- Mechanical Manipulation Studies
 - Focus on **particle size**, which may influence opioid extractability
 - Ordinary tools/methods should be employed in testing, eg, scoops, sifters, and coffee grinders
- Effect of heat and cold on mechanical manipulation
- Solubility Studies
 - Determine ease of **solubility** with various solvents (eg, water, fingert, ethanol, isopropyl alcohol, acetone, mineral spirits)
- Route-Specific Evaluation
 - Snorting**: particle size distribution
 - Smoking**: vaporization temperature
 - Injection**: opioid concentration in small injection volume and viscosity of injection fluid

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FDA Guidance for Laboratory Manipulation and Extraction Studies

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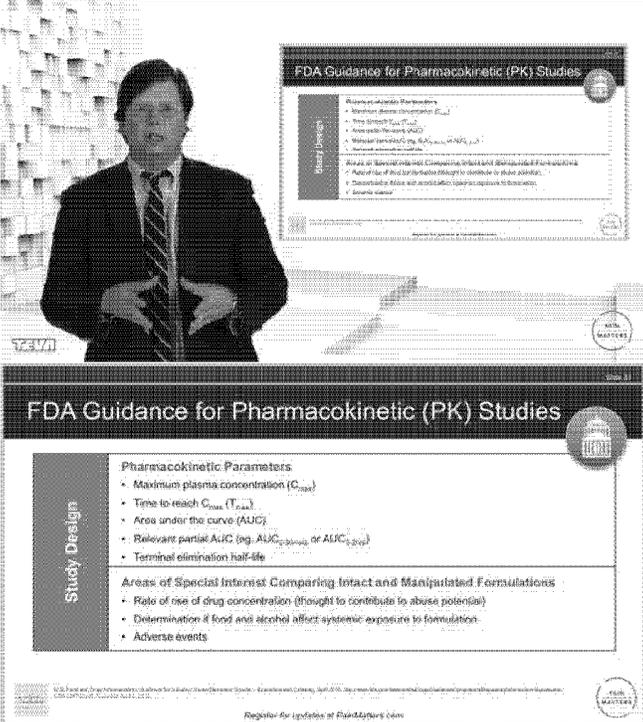
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Brennan

Let's look carefully at the manipulation studies that have been outlined by the FDA. The goal of this type of study is to see, through physical or chemical manipulation, if a drug can be easily extracted from the formulation.

These studies look at particle size and determine if a small enough particle of active drug can be extracted through various methods (including crushing, grinding, hammering, chemical reactions, and changing temperature). In other words, think of whatever a closet chemist might try to do to get that active drug out of the delivery system.

Let me emphasize this again. Remember, the molecules we're using are the same 13 or so molecules that are available in the United States that are deemed opioid analgesics. So it's not the molecule itself that's being evaluated. What we're looking at are the formulations carrying those molecules. Can those formulations protect and make it so the drug is more difficult to be

		<p>used in ways other than intended?</p> <p>And the studies also include, as I mentioned, solubility studies and we're trying to target three specific means of abuse: snorting, smoking, and injecting. Why are these three the types mentioned by the FDA? Because these are the approaches more often linked to substance abuse and addiction.</p>
<p>31</p>	 <p>The video frame shows a man in a dark suit and tie speaking. Behind him is a presentation slide titled "FDA Guidance for Pharmacokinetic (PK) Studies". The slide is divided into two main sections: "Study Design" and "Areas of Special Interest Comparing Intact and Manipulated Formulations".</p> <p>Study Design</p> <ul style="list-style-type: none"> Pharmacokinetic Parameters <ul style="list-style-type: none"> Maximum plasma concentration (C_{max}) Time to reach C_{max} (T_{max}) Area under the curve (AUC) Relevant partial AUC (eg. AUC_{0-2h} or AUC_{0-4h}) Terminal elimination half-life Areas of Special Interest Comparing Intact and Manipulated Formulations <ul style="list-style-type: none"> Rate of rise of drug concentration (thought to contribute to abuse potential) Determination if food and alcohol affect systemic exposure to formulation Adverse events <p>At the bottom of the slide, it says "Register for updates at PainMatters.com".</p>	<p>Brennan</p> <p>The second type of study that I mentioned earlier are PK studies. So for those of you who can remember back to medical school, pharmacokinetics look at how a drug acts in the system by looking at plasma concentration.</p> <p>So we're interested at looking at maximum plasma concentration, the time to reach this maximum, the total area under the curve, a relevant partial area under the curve, which we think is very important in substance abuse that is, how quickly does the drug get absorbed, and what's the terminal elimination half-life?</p> <p>What's very important in these trials is to try and understand if manipulation of the drug has an effect on the rate of rise of drug concentration. We want to determine if other substances, benign substances (food, alcohol, water, other common solutions, such as soda) might affect the way the drug is ultimately absorbed, and also collect adverse events.</p>

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Study Assessments

Measurements of interest

- Drug liking (eg, "How much did you like the drug?")
- Good effects (eg, euphoria)
- Bad effects (eg, specific adverse events)
- Likelihood to use drug again (eg, "How likely are you to use this drug again?")

Bipolar Scale

Strong dislike Neither like nor dislike Strong liking

0 100

VAS Score

* Except where otherwise specified, this guidance is for human studies (HDS) studies.

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FDA Guidance for CAP* Studies

Measurements of interest

- Drug liking (eg, "How much did you like the drug?")
- Good effects (eg, euphoria)
- Bad effects (eg, specific adverse events)
- Likelihood to use drug again (eg, "How likely are you to use this drug again?")

Bipolar Scale

Strong dislike Neither like nor dislike Strong liking

0 100

VAS Score

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FDA Guidance for CAP* Studies

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Brennan

Let's take a look at what are known in the guidance as CAP, or Clinical Abuse Potential, studies. These are what we used to refer to as the human abuse liability potential of a drug, measured in a way that many clinicians find interesting.

This involves exposing recreational non-dependent individuals to the opioid formulation using well-controlled studies. So people who aren't physically dependent on an opioid, but will use them recreationally and have enough experience to understand what the normal high of an opioid would feel like.

And what the subjects are asked to do is tell us how much they like the drug. So they're given a visual analog scale, similar to this bipolar scale on the slide, where the individual is asked after being exposed to the drug how much they like it or dislike it.

And they're asked questions, questions that you and I won't ask in our clinics. I mean, we may ask our patients about adverse events, but here we're trying to tease out different information from these recreational drug abusers and then the all-important question, how likely are you to use this drug if you can get it?

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The screen displays the following content:

FDA Guidance for Postmarket Studies

Study Characteristics

- Use outcomes that provide meaningful measures of abuse deterrence
- Produce estimates of abuse deterrence that are nationally representative, or are based on data from a large geographic region
- Assess overall and route-specific abuse and abuse deterrence
- Are sufficiently powered to assess meaningful changes in drug abuse

General Characteristics

- Use outcomes that provide meaningful measures of abuse deterrence
- Produce estimates of abuse deterrence that are nationally representative, or are based on data from a large geographic region
- Assess overall and route-specific abuse and abuse deterrence
- Are sufficiently powered to assess meaningful changes in drug abuse

Study Population

- Should be carefully selected (ie, relevant to real-world abuse)
- At least one study should include high-risk subjects (eg, drug abusers)

Use of Comparators

- Comparators are critical to rule out other factors (eg, educational interventions, law enforcement changes)
- Other opioids as comparators are encouraged

Brennan

The fourth category describes postmarket studies to be conducted in order to examine if a formulation is likely to decrease abuse in the community.

The goals are to try and provide estimates of how the drug is being abused, whether it's being snorted or injected, and has this formulation demonstrated a reduction in abuse.

These studies require sufficient numbers to determine whether or not there is a real or an artificial effect, and as such, study populations are going to have to be carefully selected to target real-world abusers.

Comparators will also be looked at to see if changes are due to the formulation or other factors, like educational programs or changes in law enforcement. There will also likely be other opioid comparators as part of these studies.

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The screen displays the following content:

Abuse-Deterrent Formulations: Crush-Resistant Pills and Capsules

How Abuse-Deterrents Work

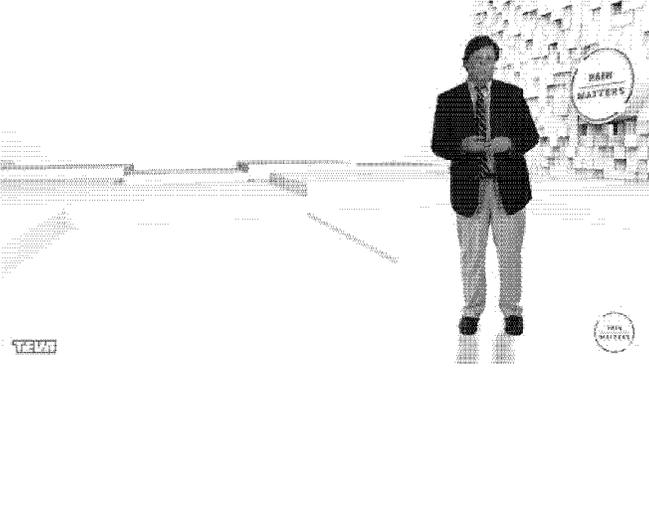
- Abuse-deterrent formulations are designed to make it difficult to crush, dissolve, or inject the drug.
- These formulations are designed to reduce the amount of drug that can be abused.
- Abuse-deterrent formulations are designed to reduce the amount of drug that can be abused.

Brennan

Now that we've reviewed the studies that may be conducted to test an abuse-deterrent opioid formulation, let's switch gears and look at some of the different approaches.

Perhaps the most common form of abuse deterrent is the crush-resistant pill and capsules. All of these have in common a process that makes it very difficult to crush

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		<p>deterrent opioids may be able to include language in their package inserts to let clinicians know what effect the formulation is likely to have on abuse and abuse potential, which will ultimately help us make better informed decisions for our patients.</p>
<p>37</p>		<p>Brennan Thank you for watching this chapter on the development of abuse-deterrent opioids. If you haven't already, please be sure to return to the main menu to watch the other chapters, including Jeff Gudin talking about the complexities we face in pain management, and Charles Argoff talking about Multi-Faceted Approach to Address Prescription Opioid Abuse.</p> <p>On behalf of all 3 faculty and Teva Pharmaceuticals, we hope you enjoyed the program and thank you for your time.</p>
	<p>Video Image</p> 	<p>Closing Music</p>