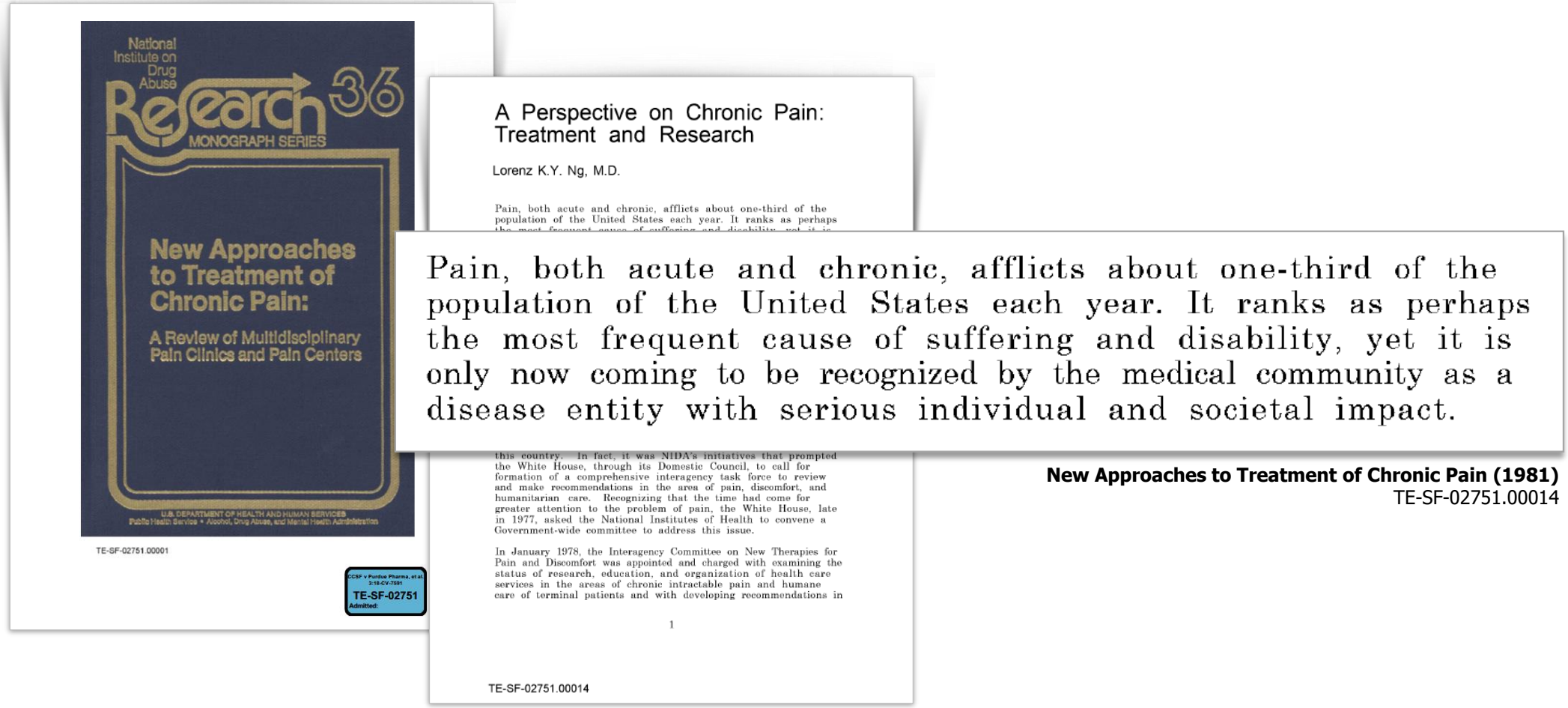
Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Cephalon, Inc., and Actavis Generic Defendants'

Cross Examination of Anna Lembke, M.D.

May 9, 2022

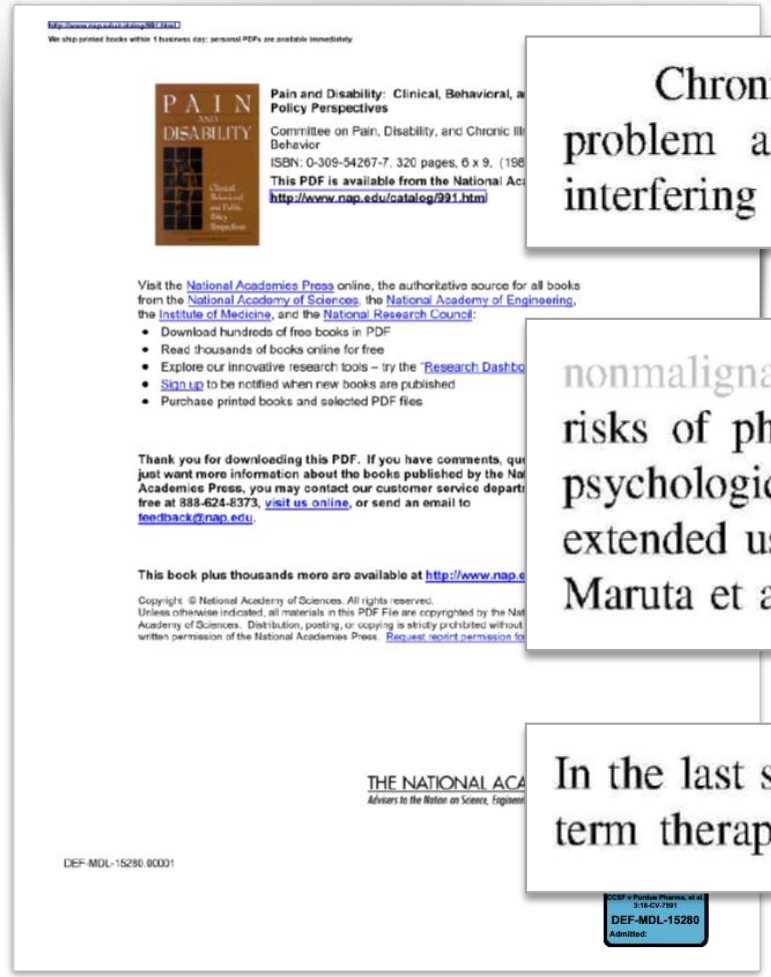
National Institute on Drug Abuse (NIDA) 1981



New Approaches to Treatment of Chronic Pain (1981)
TE-SF-02751.00014

TCA Defendants Court Exhibit 00001.00002

National Academy of Sciences, Engineering, and Mathematics (NASEM) (1987)



Chronic pain, especially musculoskeletal pain, is a common health problem afflicting a substantial proportion of the adult population and interfering with every aspect of their lives. The course of chronic pain and

Pain and Disability, DEF-MDL-15280.00024 (1987)

nonmalignant chronic pain. Until very recently it was generally thought that the risks of physical and psychological drug dependence, drug abuse, increased psychological distress, and impaired cognition were too great to warrant the extended use of narcotic analgesics for severe chronic pain (see, for example, Maruta et al., 1979; Maruta and Swanson, 1981; Medina and Diamond, 1977).

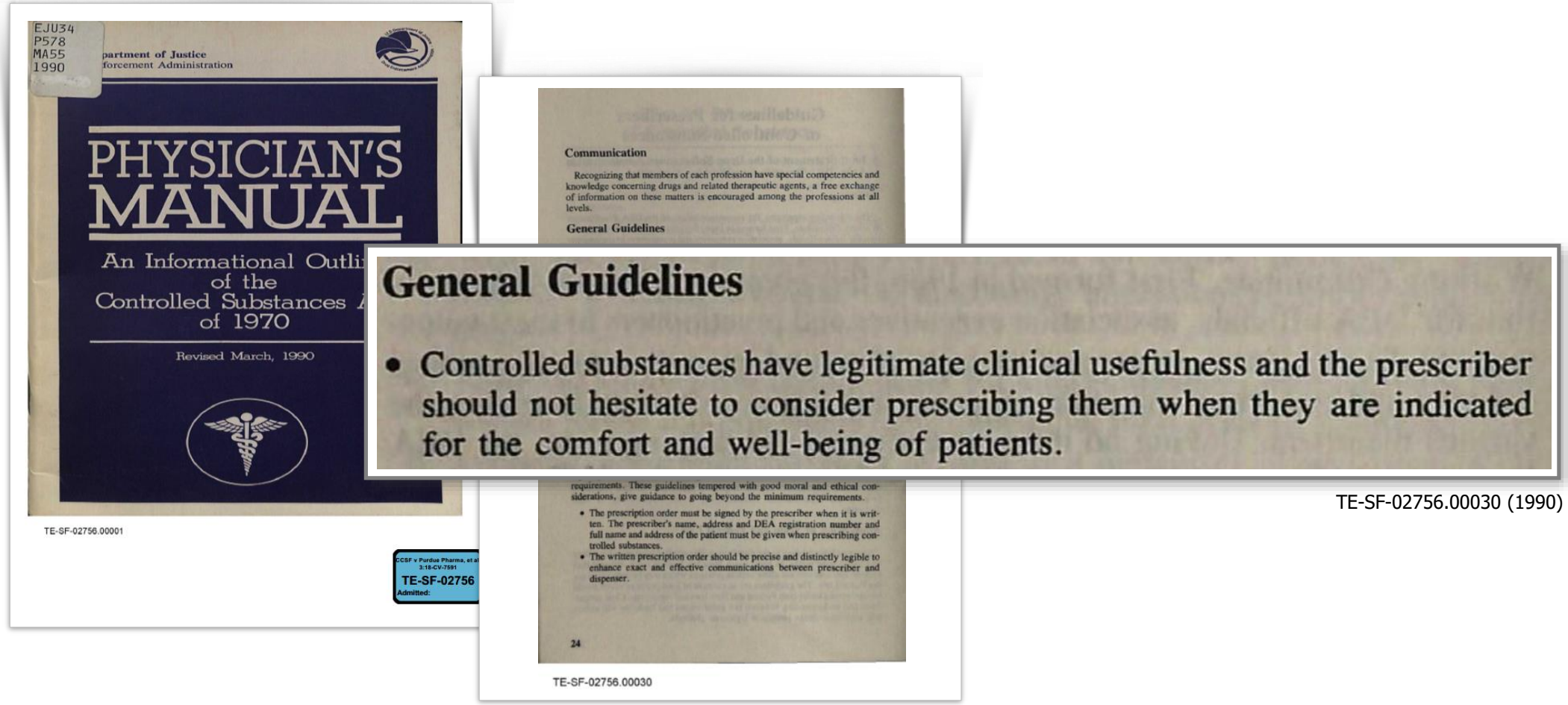
Pain and Disability, DEF-MDL-15280.00216 (1987)

In the last several years, however, there have been reports indicating that long-term therapy with these drugs can be successful. For example, Portenoy and

Pain and Disability, DEF-MDL-15280.00216 (1987)

TCA Defendants Court Exhibit 00001.00003

Drug Enforcement Agency Physician's Manual (1990)



TE-SF-02756.00030 (1990)

TCA Defendants Court Exhibit 00001.00004

California Intractable Pain Act (1990)
Bus. & Prof. Code § 2241.5

West's Ann.Cal.Bus. & Prof.Code § 2241.5

§ 2241.5. Prescription or administration of controlled substances; intractable pain; application; denial, revocation, suspension of physician's and surgeon's license

(a) Notwithstanding any other provision of law, a physician and surgeon may prescribe or administer controlled substances to a person in the course of the physician and surgeon's treatment of that person for a diagnosed condition causing intractable pain.

* * *

Credits

(Added by Stats.1990, c. 1588 (S.B.1802), § 1. Amended by Stats.1994, c. 222 (S.B.1402), § 1.)

California Intractable Pain Act (Amended 2006, 2015)
Bus. & Prof. Code § 2241.5

West's Ann.Cal.Bus. & Prof.Code § 2241.5

§ 2241.5. Prescription or administration of dangerous drugs or prescription controlled substances for treatment of pain or condition causing pain

(a) A physician and surgeon may prescribe for, or dispense or administer to, a person under his or her treatment for a medical condition dangerous drugs or prescription controlled substances for the treatment of pain or a condition causing pain, including, but not limited to, intractable pain.

* * *

Credits

(Added by Stats.2006, c. 350 (A.B.2198), § 5. Amended by Stats.2015, c. 719 (S.B.643), § 3, eff. Jan. 1, 2016.)

California Intractable Pain Act (1990)
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(a) Notwithstanding any other provision of law, a physician and surgeon may prescribe or administer controlled substances to a person in the course of the physician and surgeon's treatment of that person for a diagnosed condition causing intractable pain.

* * *

(c) No physician and surgeon shall be subject to disciplinary action by the board for prescribing or administering controlled substances in the course of treatment of a person for intractable pain.

* * *

Credits

(Added by Stats.1990, c. 1588 (S.B.1802), § 1. Amended by Stats.1994, c. 222 (S.B.1402), § 1.)

California Pain Patients' Bill of Rights (1997)
Health & Safety Code §§ 124960, 124961

West's Ann.Cal.Health & Safety Code § 124960

§ 124960. Findings and declarations; opiate drugs; pain management

The Legislature finds and declares all of the following:

(a) The state has a right and duty to control the illegal use of opiate drugs.

(b) Inadequate treatment of acute and chronic pain originating from cancer or noncancerous conditions is a significant health problem.

(c) For some patients, pain management is the single most important treatment a physician can provide.

* * *

(f) In the hands of knowledgeable, ethical, and experienced pain management practitioners, opiates administered for severe acute and severe chronic intractable pain can be safe.

California Pain Patients' Bill of Rights (1997)
Health & Safety Code §§ 124960, 124961

West's Ann.Cal.Health & Safety Code § 124960

§ 124960. Findings and declarations; opiate drugs; pain management

Currentness

The Legislature finds and declares all of the following:

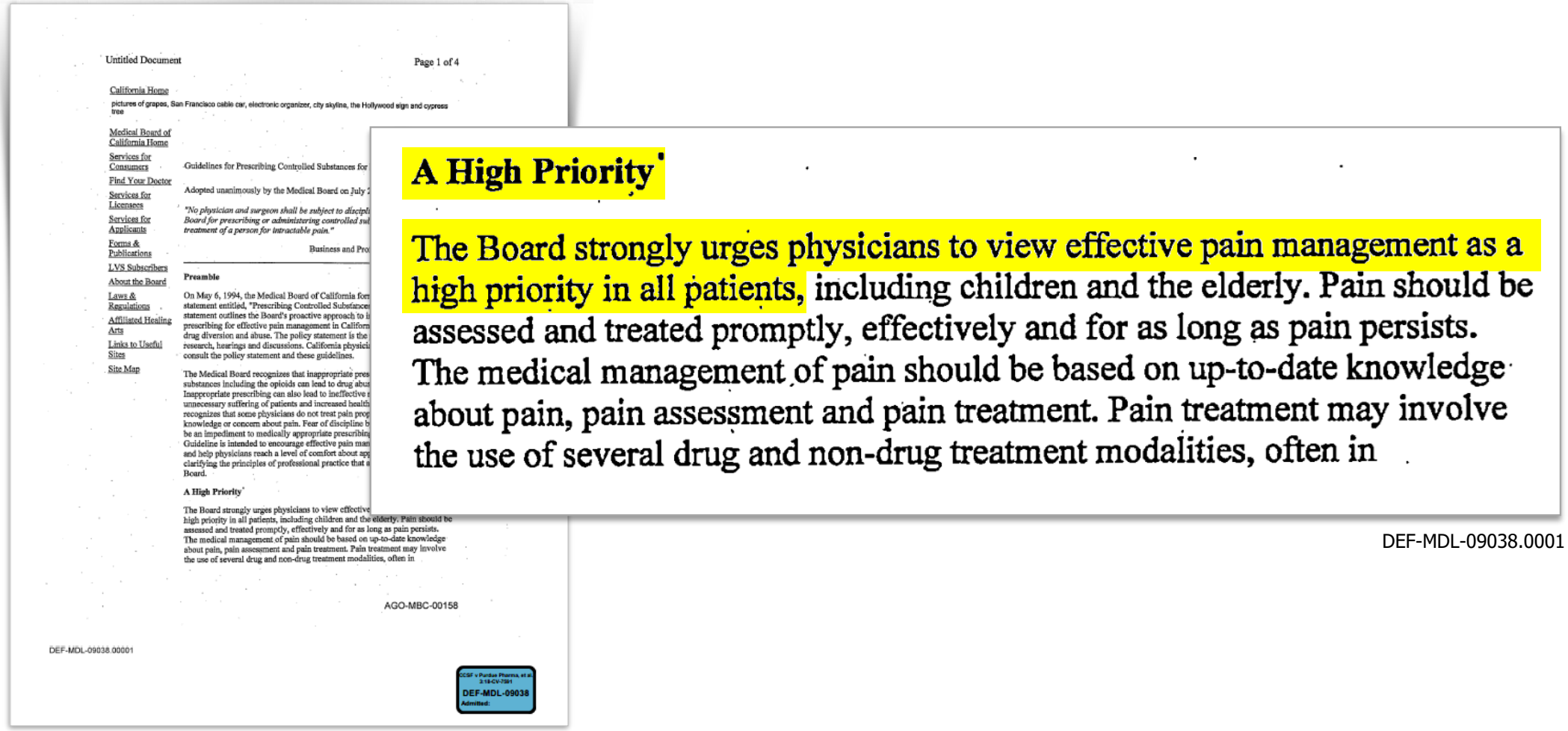
* * *

(d) A patient suffering from severe chronic intractable pain should have access to proper treatment of his or her pain.

* * *

(k) The patient's physician may refuse to prescribe opiate medication for a patient who requests the treatment for severe chronic intractable pain. However, that physician shall inform the patient that there are physicians who specialize in the treatment of severe chronic intractable pain with methods that include the use of opiates.

Medical Board of California (1994)
Guidelines for Prescribing Controlled Substances for Intractable Pain



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Page 1 of 4

California Home

pictures of grapes, San Francisco cable car, electronic organizer, city skyline, the Hollywood sign and cypress tree

Medical Board of California Home

Services for Consumers

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Services for Licensees

Services for Applicants

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About the Board

Laws & Regulations

Affiliated Healing Arts

Links to Useful Sites

Site Map

Guidelines for Prescribing Controlled Substances for

Adopted unanimously by the Medical Board on July

"No physician and surgeon shall be subject to disciplin Board for prescribing or administering controlled sub treatment of a person for intractable pain."

Business and Pro

Preamble

On May 6, 1994, the Medical Board of California for statement entitled, "Prescribing Controlled Substance statement outlines the Board's proactive approach to i prescribing for effective pain management in Californ drug diversion and abuse. The policy statement is the research, hearings and discussions. California physici consult the policy statement and these guidelines.

The Medical Board recognizes that inappropriate pres substances including the opioids can lead to drug abus Inappropriate prescribing can also lead to ineffective unnecessary suffering of patients and increased health recognizes that some physicians do not treat pain prog knowledge or concern about pain. Fear of discipline b be an impediment to medically appropriate prescribin Guideline is intended to encourage effective pain man and help physicians reach a level of comfort about ap clarifying the principles of professional practice that Board.

A High Priority

The Board strongly urges physicians to view effective high priority in all patients, including children and the elderly. Pain should be assessed and treated promptly, effectively and for as long as pain persists. The medical management of pain should be based on up-to-date knowledge about pain, pain assessment and pain treatment. Pain treatment may involve the use of several drug and non-drug treatment modalities, often in

AGO-MBC-00158

DEF-MDL-09038.00001

CCSF v Purdue Pharma, et al. 3:18-CV-7591

DEF-MDL-09038

Admitted:

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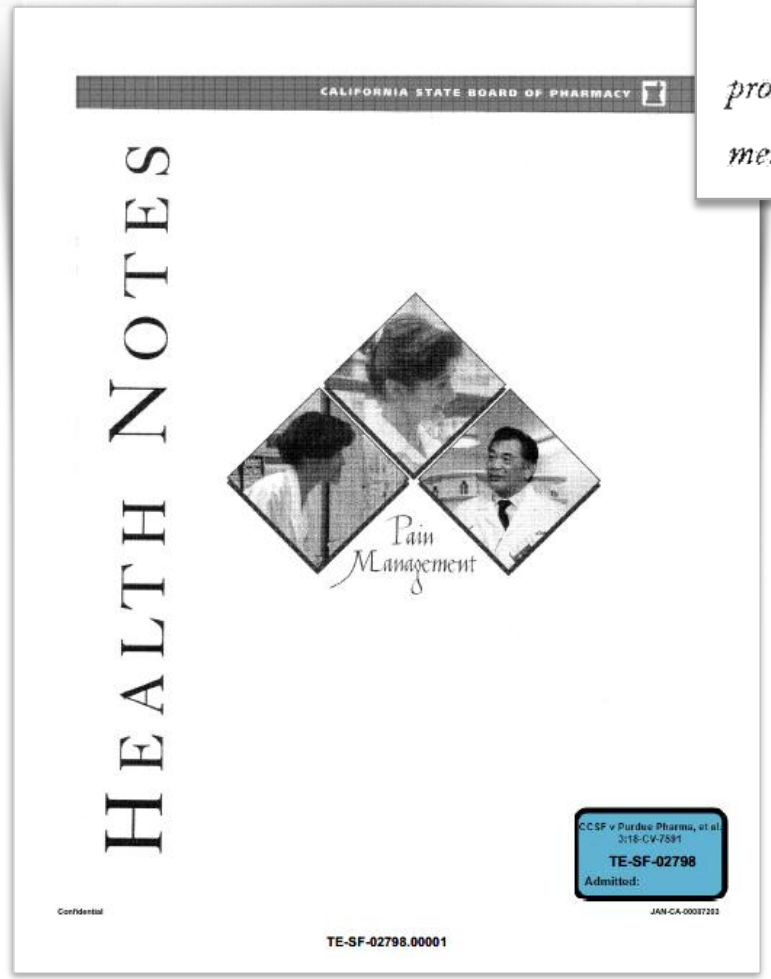
DEF-MDL-09038.0001

TCA Defendants Court Exhibit 00001.00010

California State Board of Pharmacy (1996)
Health Notes



TE-SF-02798.00001

HEALTH NOTES is designed to be a reference source for pharmacists and other health care providers to use in helping patients better understand their illness, comply with prescribed treatment regimens and take greater responsibility for their health.

TE-SF-02798.00003

ROLE OF OPIOIDS IN PAIN MANAGEMENT

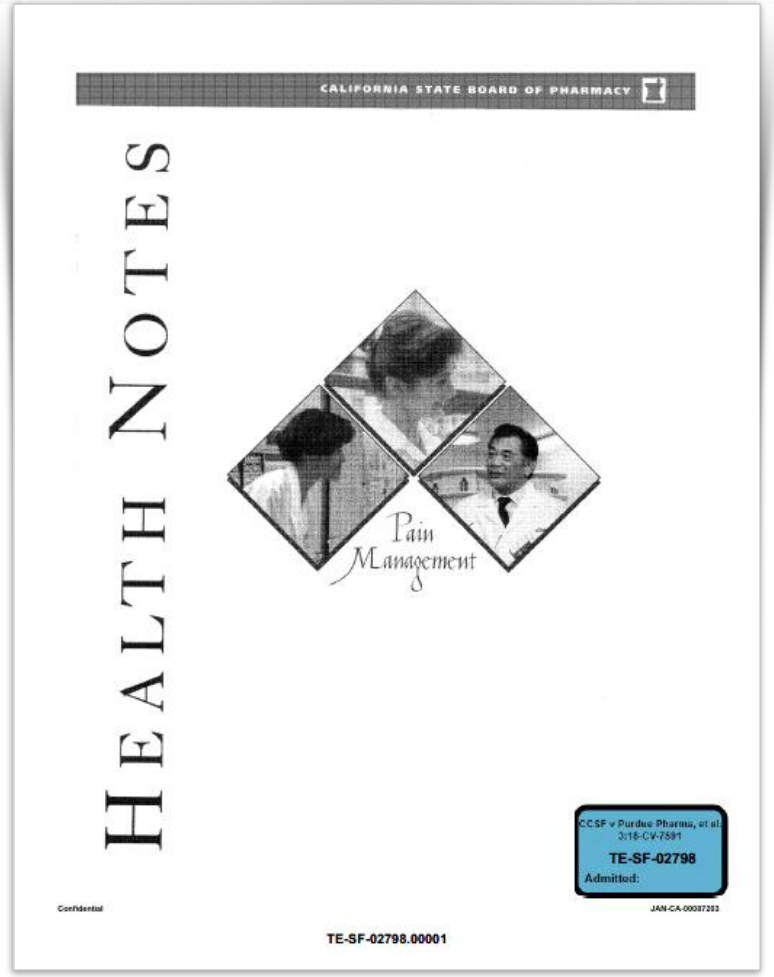
Many patients with cancer or chronic medical conditions experience moderate to severe pain that is often inappropriately treated or undermedicated. Pain can have a negative effect on the patient's health and quality of life resulting in needless suffering, emotional distress, loss of productivity and possibly slower recovery from illness, injury, and disease.

Although there have been significant advances in knowledge about pain and the use of opioids and other medications in pain management, many licensed healthcare professionals prescribe, dispense, or administer these medications suboptimally. There is a misconception by patients, the public, and some licensed healthcare providers that opioids are "bad" drugs because opioids are often associated with drug abuse, addiction, and criminal activity. Studies have shown that opioids used appropriately for pain management have an extremely low potential for abuse.

TE-SF-02798.00004

TCA Defendants Court Exhibit 00001.00011

California State Board of Pharmacy (1996)
Health Notes



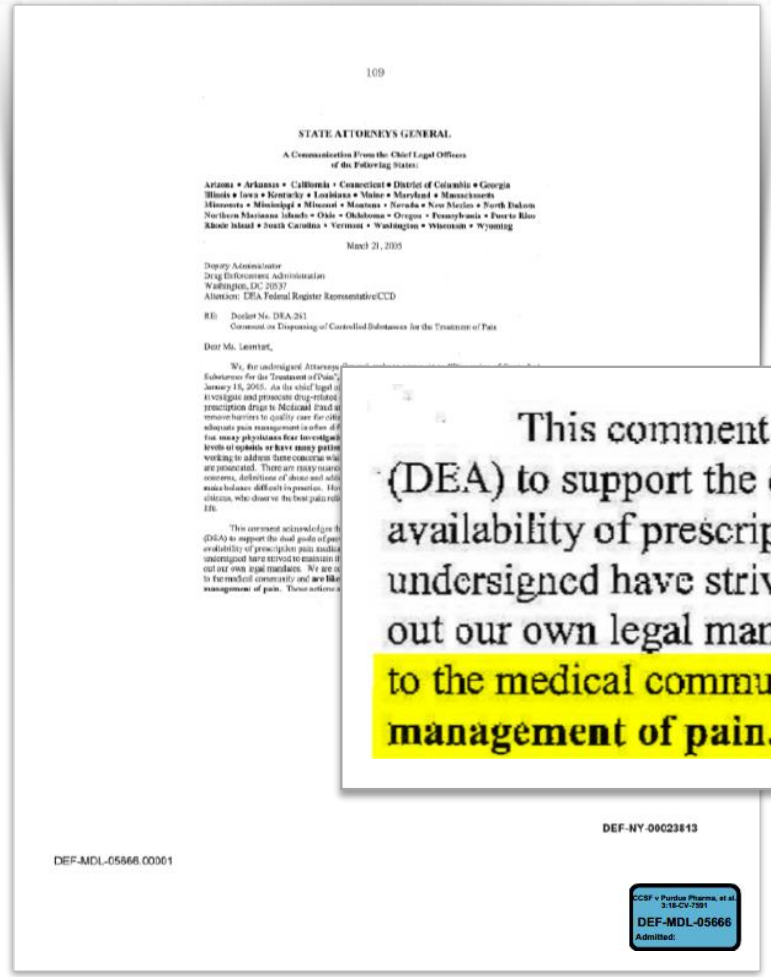
CONCLUSION

Recognition of the utility of opioids and other controlled substance drugs for the treatment of pain resulting from a variety of conditions is well established. The need for regulators and practitioners to understand this use, and to adopt laws, policies, and practices is self-evident if patients are to receive relief from pain which is now medically possible. In addition, pharmacists must understand their role in the on-going monitoring and assessment of patients' pain management. Working cooperatively, the Board of Pharmacy and the profession can ensure that opioids and other controlled substance drugs are used appropriately and effectively.

TE-SF-02798.00005

TCA Defendants Court Exhibit 00001.00012

California Attorney General Letter to DEA (2005)



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STATE ATTORNEYS GENERAL

A Communication From the Chief Legal Officers of the Following States:

Arizona • Arkansas • California • Connecticut • District of Columbia • Georgia Illinois • Iowa • Kentucky • Louisiana • Maine • Maryland • Massachusetts Minnesota • Mississippi • Missouri • Montana • Nevada • New Mexico • North Dakota Northern Mariana Islands • Ohio • Oklahoma • Oregon • Pennsylvania • Puerto Rico Rhode Island • South Carolina • Vermont • Washington • Wisconsin • Wyoming

March 21, 2005

Deputy Administrator
Drug Enforcement Administration
Washington, DC 20537
Attention: DEA Federal Register Representative/CCD

RE: Docket No. DEA-261
Comment on Dispensing of Controlled Substances for the Treatment of Pain

Dear Ms. Leonhart,

We, the undersigned Attorneys

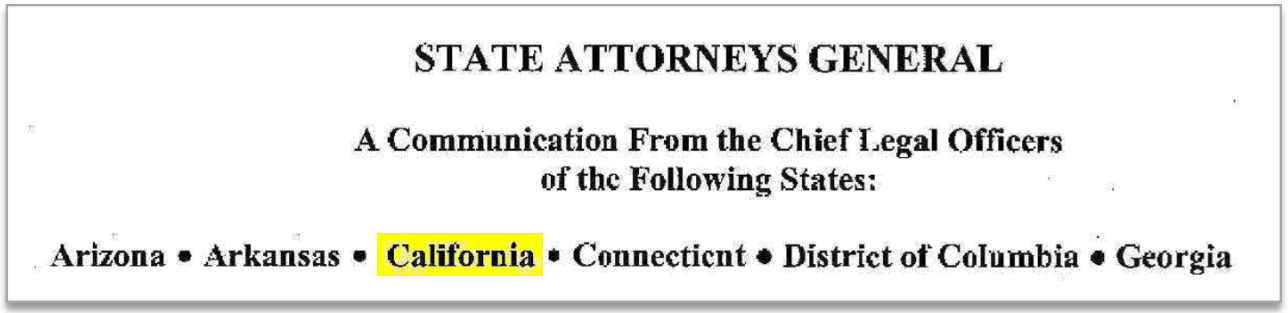
This comment acknowledges the past efforts of the Drug Enforcement Administration (DEA) to support the dual goals of preventing drug abuse and diversion and ensuring the availability of prescription pain medications to those who are legitimately in need of them. The undersigned have strived to maintain the delicate balance between these two goals in carrying out our own legal mandates. We are concerned that recent DEA actions send mixed messages to the medical community and are likely to discourage appropriate prescribing for the management of pain. Those actions also put DEA at odds with advances in state policies

DEF-NY-00023813

DEF-MDL-05666.00001

CCSF v Purdue Pharma, et al.
3:18-CV-7591
DEF-MDL-05666
Admitted:

DEF-MDL-05666.00001



STATE ATTORNEYS GENERAL

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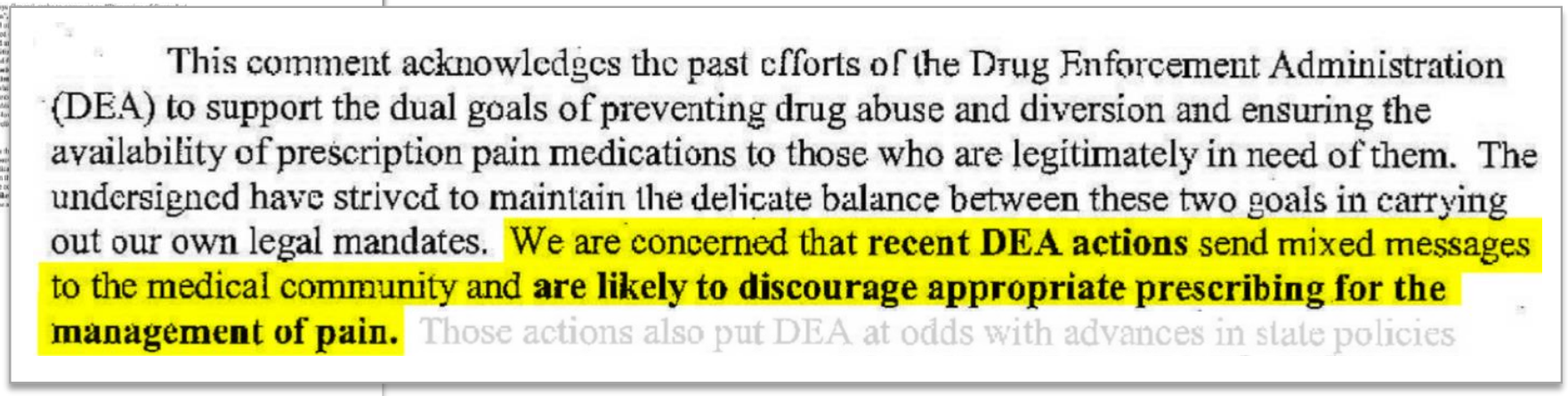
DEF-MDL-05666.00001



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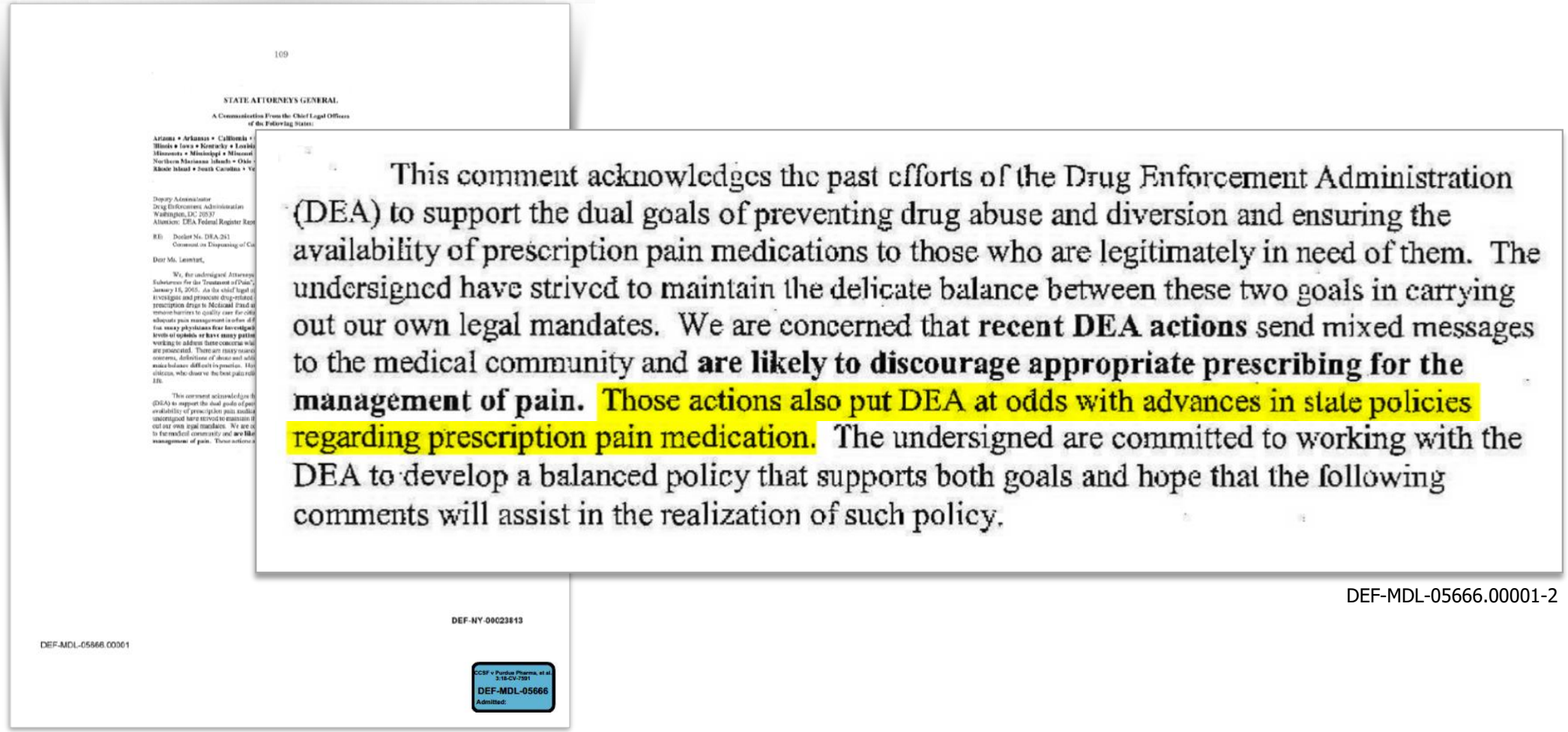
DEF-MDL-05666.00001

TCA Defendants Court Exhibit 00001.00013

California Attorney General Letter to DEA (2005)



109

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DEF-NY-00023813

DEF-MDL-05666.00001

CCSF v Purdue Pharma, et al. 3:18-CV-7591
DEF-MDL-05666
Admitted:

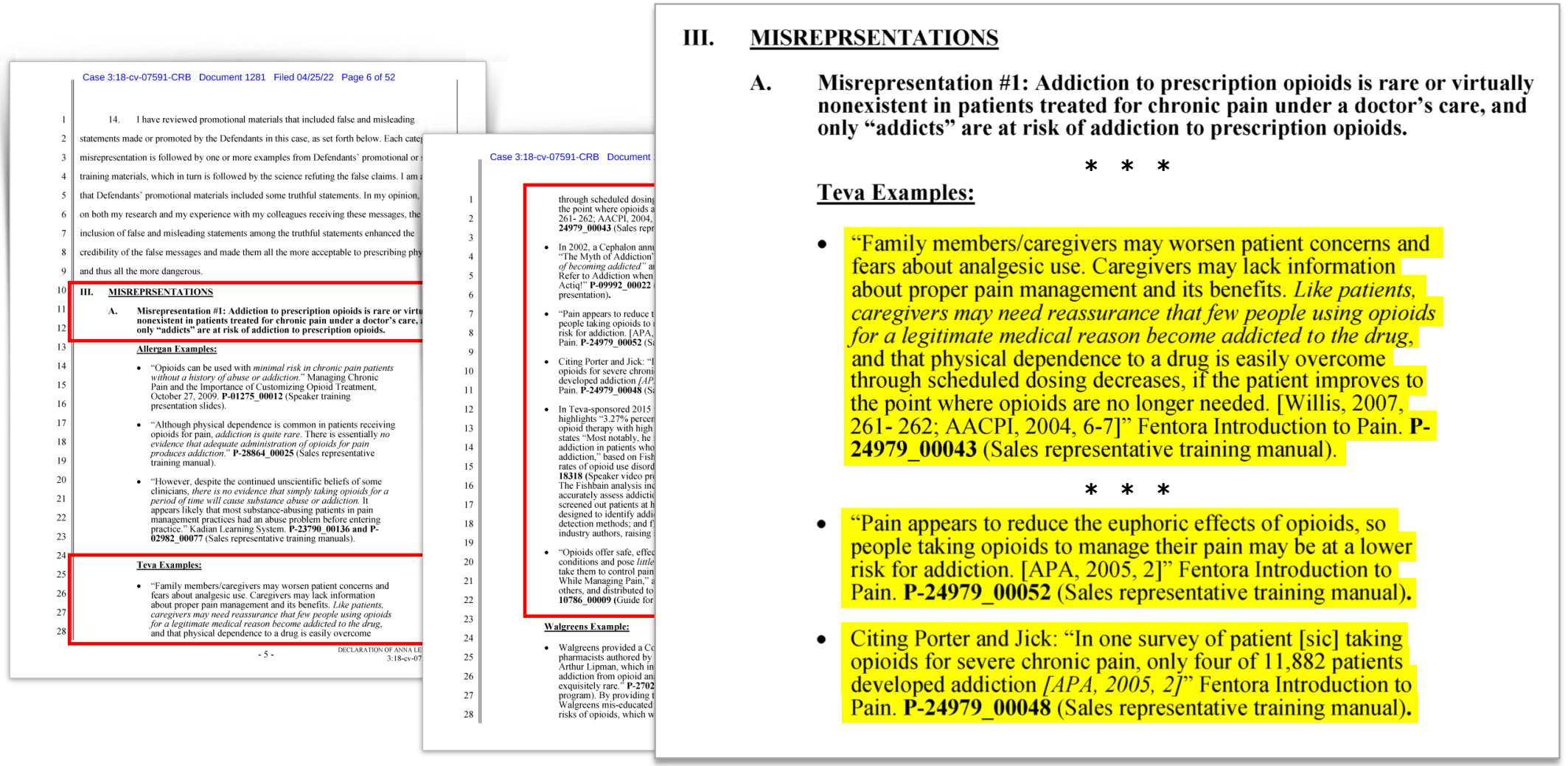
DEF-MDL-05666.00001-2

TCA Defendants Court Exhibit 00001.00014

Dr. Lembke's "Misrepresentations"

1	"Addiction to prescription opioids is rare or virtually nonexistent in patients treated for chronic pain under a doctor's care, and only 'addicts' are at risk of addition to prescription opioids."
2	"There is no clinical 'ceiling dose' of prescription opioids, in contrast to other pain relief medications, so opioids can be uptitrated without concern of harm."
3	"Drug-seeking behavior in patients receiving opioid therapy is not a sign of addiction but rather pseudoaddiction, and these patients are experiencing under-treated pain requiring more opioids."
4	"Opioids are effective, first-line treatment for chronic pain."
5	"Dependence is a benign and easily treated condition, dependence on opioids is no different from dependence on other drugs, like blood-pressure medications,"
	"[B]reakthrough pain is not a sign of decreasing efficacy, but a sign of needing more potent and faster acting opioids on top of longer-acting opioids."
6	"Screening tools can identify who will become addicted."
7	"Abuse deterrent formulations decrease risk and addiction."

Declaration of Anna Lembke, M.D.



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14. I have reviewed promotional materials that included false and misleading statements made or promoted by the Defendants in this case, as set forth below. Each categ misrepresentation is followed by one or more examples from Defendants' promotional or s training materials, which in turn is followed by the science refuting the false claims. I am a that Defendants' promotional materials included some truthful statements. In my opinion, on both my research and my experience with my colleagues receiving these messages, the inclusion of false and misleading statements among the truthful statements enhanced the credibility of the false messages and made them all the more acceptable to prescribing phy and thus all the more dangerous.

III. MISREPRSENTATIONS

A. **Misrepresentation #1: Addiction to prescription opioids is rare or virtu nonexistent in patients treated for chronic pain under a doctor's care, only "addicts" are at risk of addiction to prescription opioids.**

Allergan Examples:

- "Opioids can be used with *minimal risk in chronic pain patients without a history of abuse or addiction.*" Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009. **P-01275_00012** (Speaker training presentation slides).
- "Although physical dependence is common in patients receiving opioids for pain, *addiction is quite rare*. There is essentially *no evidence that adequate administration of opioids for pain produces addiction.*" **P-28864_00025** (Sales representative training manual).
- "However, despite the continued unscientific beliefs of some clinicians, *there is no evidence that simply taking opioids for a period of time will cause substance abuse or addiction.* It appears likely that most substance-abusing patients in pain management practices had an abuse problem before entering practice." Kadian Learning System. **P-23790_00136 and P-02982_00077** (Sales representative training manuals).

Teva Examples:

- "Family members/caregivers may worsen patient concerns and fears about analgesic use. Caregivers may lack information about proper pain management and its benefits. *Like patients, caregivers may need reassurance that few people using opioids for a legitimate medical reason become addicted to the drug,* and that physical dependence to a drug is easily overcome

- 5 -

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3:18-cv-07

Case 3:18-cv-07591-CRB Document

through scheduled dosing
the point where opioids a
261- 262; AACPI, 2004,
24979_00043 (Sales repr

- In 2002, a Cephalon annu "The Myth of Addiction *of becoming addicted"* a Refer to Addiction when Actiq!" **P-09992_00022** presentation).
- "Pain appears to reduce t people taking opioids to risk for addiction. [APA, Pain. **P-24979_00052** (Sa
- Citing Porter and Jick: "I opioids for severe chroni developed addiction *[AP* Pain. **P-24979_00048** (Sa
- In Teva-sponsored 2015 highlights "3.27% percen opioid therapy with high states "Most notably, he addiction in patients who addiction," based on Fish rates of opioid use disord **18318** (Speaker video pr The Fishbain analysis inc accurately assess addicti screened out patients at h designed to identify addi detection methods; and f industry authors, raising
- "Opioids offer safe, effec conditions and pose *little* take them to control pain While Managing Pain," a others, and distributed to **10786_00009** (Guide for

Walgreens Example:

- Walgreens provided a Co pharmacists authored by Arthur Lipman, which in addiction from opioid an exquisitely rare." **P-2702** program). By providing t Walgreens mis-educated risks of opioids, which w

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* * *

Teva Examples:

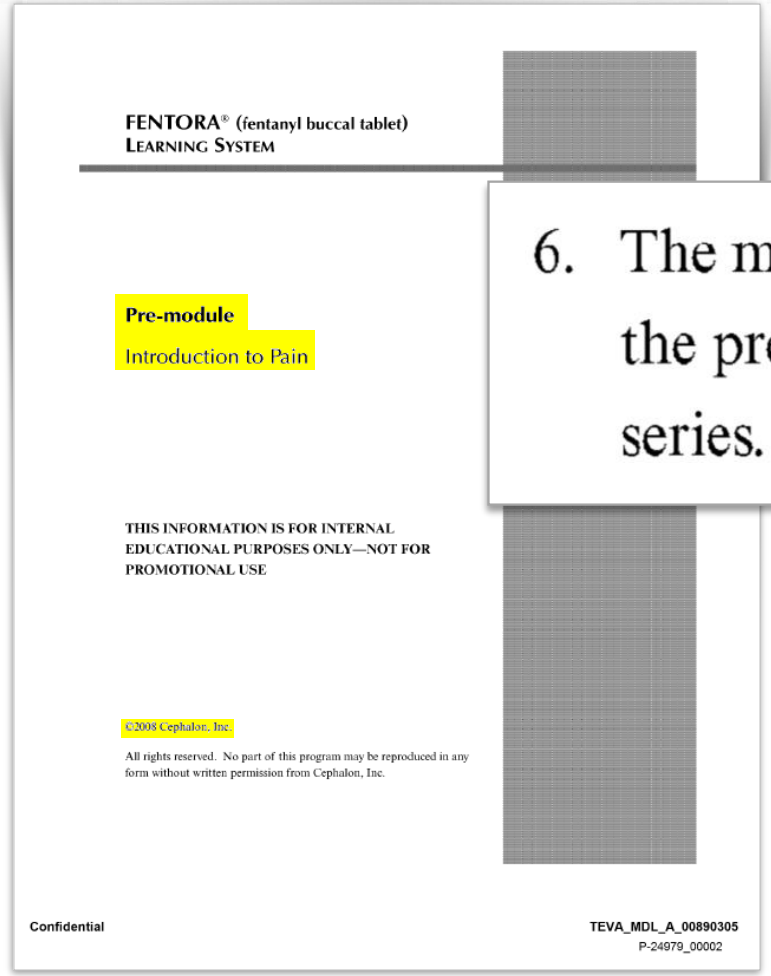
- "Family members/caregivers may worsen patient concerns and fears about analgesic use. Caregivers may lack information about proper pain management and its benefits. *Like patients, caregivers may need reassurance that few people using opioids for a legitimate medical reason become addicted to the drug,* and that physical dependence to a drug is easily overcome through scheduled dosing decreases, if the patient improves to the point where opioids are no longer needed. [Willis, 2007, 261- 262; AACPI, 2004, 6-7]" Fentora Introduction to Pain. **P-24979_00043** (Sales representative training manual).

* * *

- "Pain appears to reduce the euphoric effects of opioids, so people taking opioids to manage their pain may be at a lower risk for addiction. [APA, 2005, 2]" Fentora Introduction to Pain. **P-24979_00052** (Sales representative training manual).
- Citing Porter and Jick: "In one survey of patient [sic] taking opioids for severe chronic pain, only four of 11,882 patients developed addiction *[APA, 2005, 2]*" Fentora Introduction to Pain. **P-24979_00048** (Sales representative training manual).

Lemke Decl. ¶ 14

Fentora Learning System: Pre-module Introduction To Pain (2008)



FENTORA® (fentanyl buccal tablet)
LEARNING SYSTEM

Pre-module

Introduction to Pain

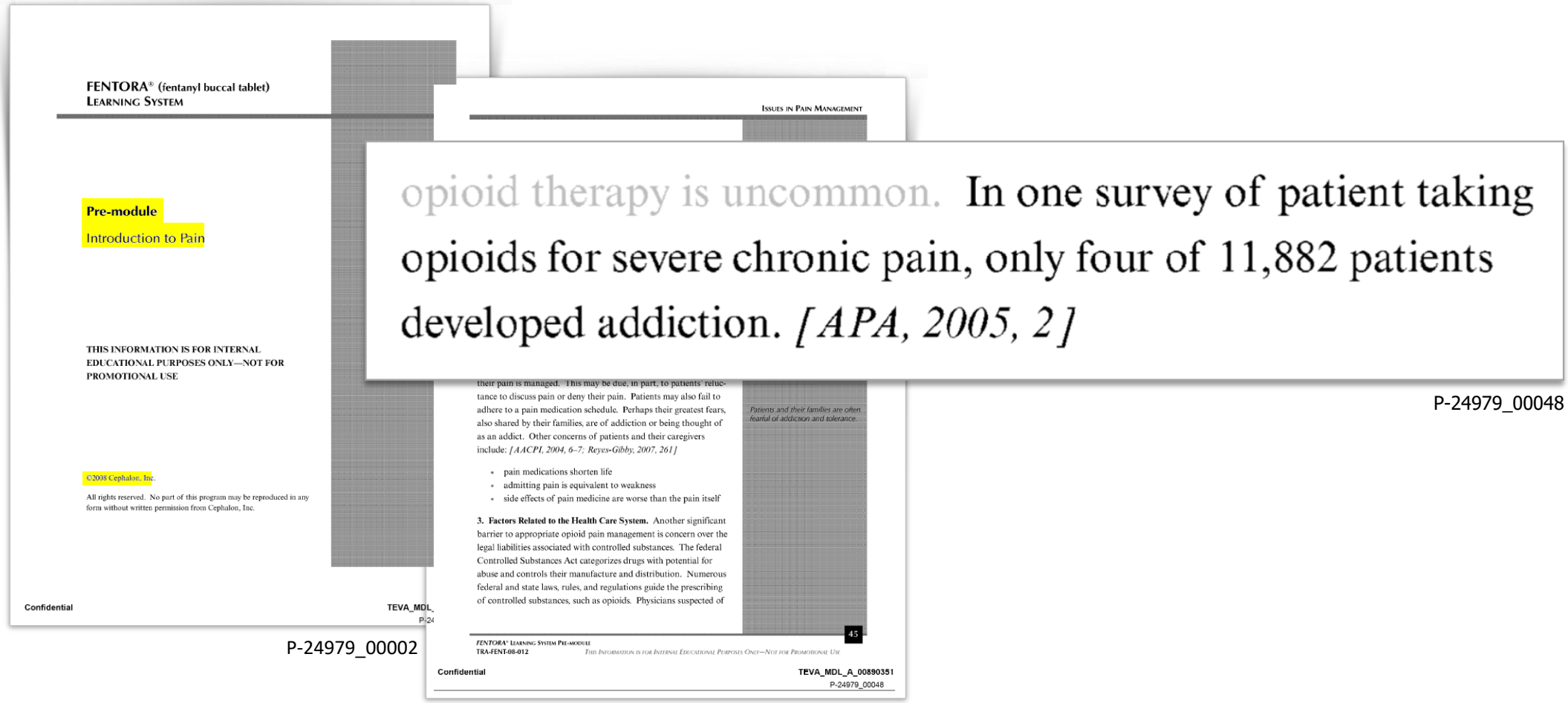
THIS INFORMATION IS FOR INTERNAL EDUCATIONAL PURPOSES ONLY—NOT FOR PROMOTIONAL USE

P-24979_00002

6. The modules build sequentially. Complete your study of the preceding module(s) before going on to the next in the series.

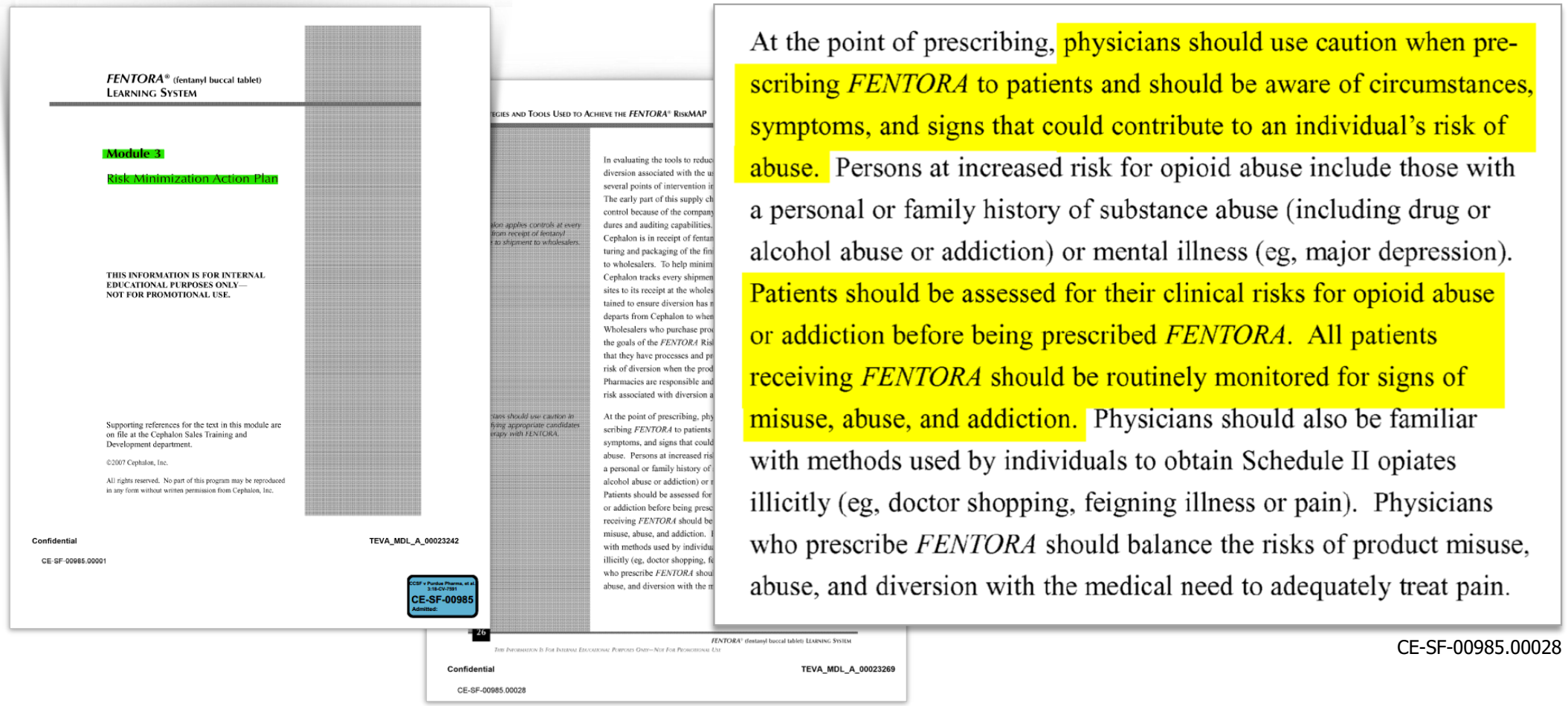
P-24979_00008

Fentora Learning System: Pre-module Introduction To Pain (2008)



TCA Defendants Court Exhibit 00001.00018

Fentora Learning System: Module 3
Risk Minimization Action Plan (2008)



FENTORA® (fentanyl buccal tablet)
LEARNING SYSTEM

Module 3

Risk Minimization Action Plan

THIS INFORMATION IS FOR INTERNAL EDUCATIONAL PURPOSES ONLY—NOT FOR PROMOTIONAL USE.

Supporting references for the text in this module are on file at the Cephalon Sales Training and Development department.

Confidential

TEVA_MDL_A_00023242

CE-SF-00985.00001

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3:18-CV-7591
CE-SF-00985
Admitted:

EGIES AND TOOLS USED TO ACHIEVE THE *FENTORA*® RISKMAP

In evaluating the tools to reduc
diversion associated with the u
several points of intervention i
The early part of this supply ch
control because of the company
dures and auditing capabilities.
Cephalon is in receipt of fentan
turing and packaging of the fin
to wholesalers. To help minim
Cephalon tracks every shipmen
sites to its receipt at the wholes
tained to ensure diversion has
departs from Cephalon to when
Wholesalers who purchase pro
the goals of the *FENTORA* Ris
that they have processes and p
risk of diversion when the prod
Pharmacies are responsible and
risk associated with diversion a

At the point of prescribing, phy
scribing *FENTORA* to patients
symptoms, and signs that could
abuse. Persons at increased ris
a personal or family history of
alcohol abuse or addiction) or
Patients should be assessed for
or addiction before being presc
receiving *FENTORA* should be
misuse, abuse, and addiction.
with methods used by individu
illicitly (eg, doctor shopping, f
who prescribe *FENTORA* shou
abuse, and diversion with the m

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FENTORA® (fentanyl buccal tablet) LEARNING SYSTEM

THIS INFORMATION IS FOR INTERNAL EDUCATIONAL PURPOSES ONLY—NOT FOR PROMOTIONAL USE

Confidential

TEVA_MDL_A_00023269

CE-SF-00985.00028

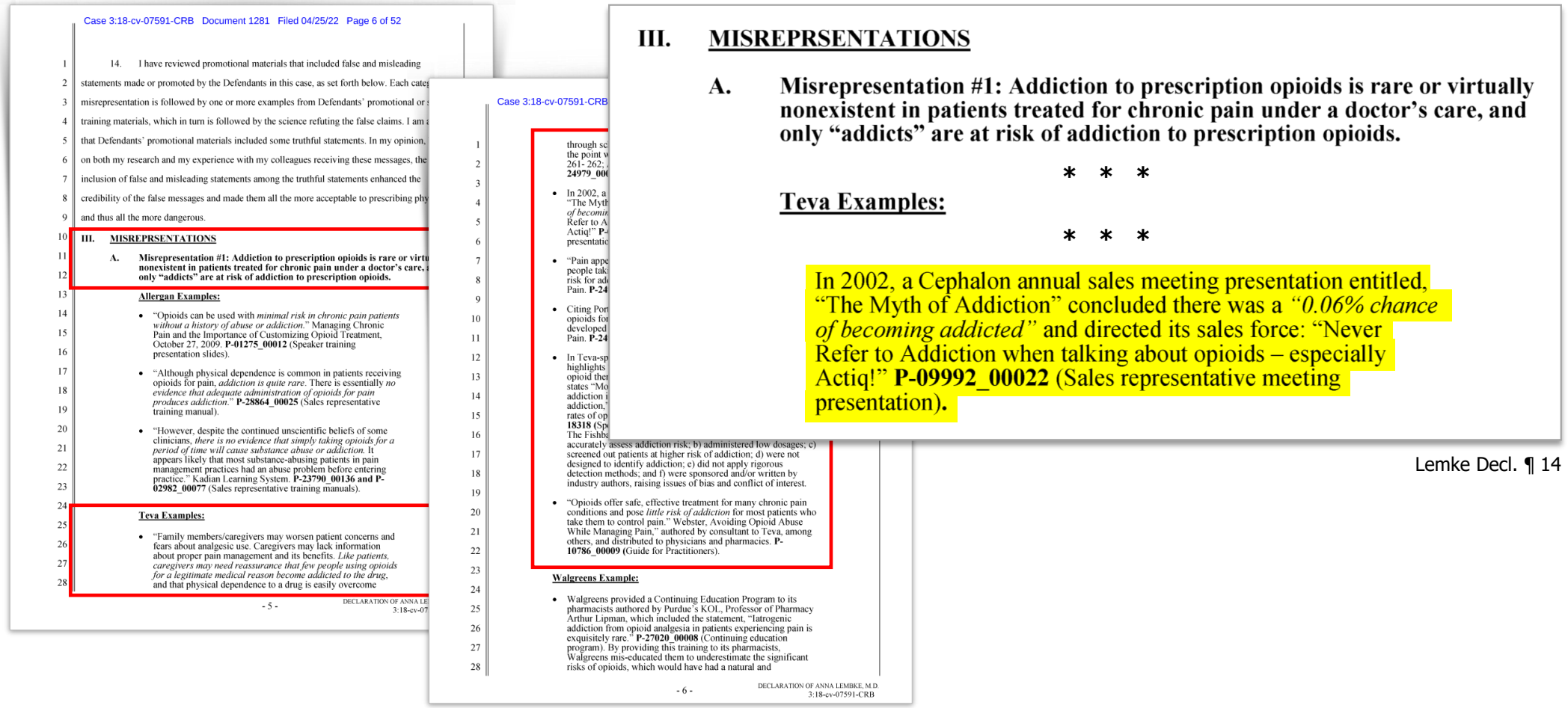
At the point of prescribing, physicians should use caution when prescribing *FENTORA* to patients and should be aware of circumstances, symptoms, and signs that could contribute to an individual's risk of abuse. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (eg, major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction before being prescribed *FENTORA*. All patients receiving *FENTORA* should be routinely monitored for signs of misuse, abuse, and addiction. Physicians should also be familiar with methods used by individuals to obtain Schedule II opiates illicitly (eg, doctor shopping, feigning illness or pain). Physicians who prescribe *FENTORA* should balance the risks of product misuse, abuse, and diversion with the medical need to adequately treat pain.

CE-SF-00985.00028

CE-SF-00985.0001

TCA Defendants Court Exhibit 00001.00019

Declaration of Anna Lembke, M.D.



Case 3:18-cv-07591-CRB Document 1281 Filed 04/25/22 Page 6 of 52

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- In 2002, a "The Myth *of becomi* Refer to A Actiq!" **P-** presentatio
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- Citing Port opioids for developed Pain. **P-24**
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- "Opioids offer safe, effective treatment for many chronic pain conditions and pose *little risk of addiction* for most patients who take them to control pain." Webster, Avoiding Opioid Abuse While Managing Pain," authored by consultant to Teva, among others, and distributed to physicians and pharmacies. **P-10786_00009** (Guide for Practitioners).

Walgreens Example:

- Walgreens provided a Continuing Education Program to its pharmacists authored by Purdue's KOL, Professor of Pharmacy Arthur Lipman, which included the statement, "Iatrogenic addiction from opioid analgesia in patients experiencing pain is exquisitely rare." **P-27020_00008** (Continuing education program). By providing this training to its pharmacists, Walgreens mis-educated them to underestimate the significant risks of opioids, which would have had a natural and

- 6 -

DECLARATION OF ANNA LEMBKE, M.D.
3:18-cv-07591-CRB

III. MISREPRSENTATIONS

A. Misrepresentation #1: Addiction to prescription opioids is rare or virtually nonexistent in patients treated for chronic pain under a doctor's care, and only "addicts" are at risk of addiction to prescription opioids.

* * *

Teva Examples:

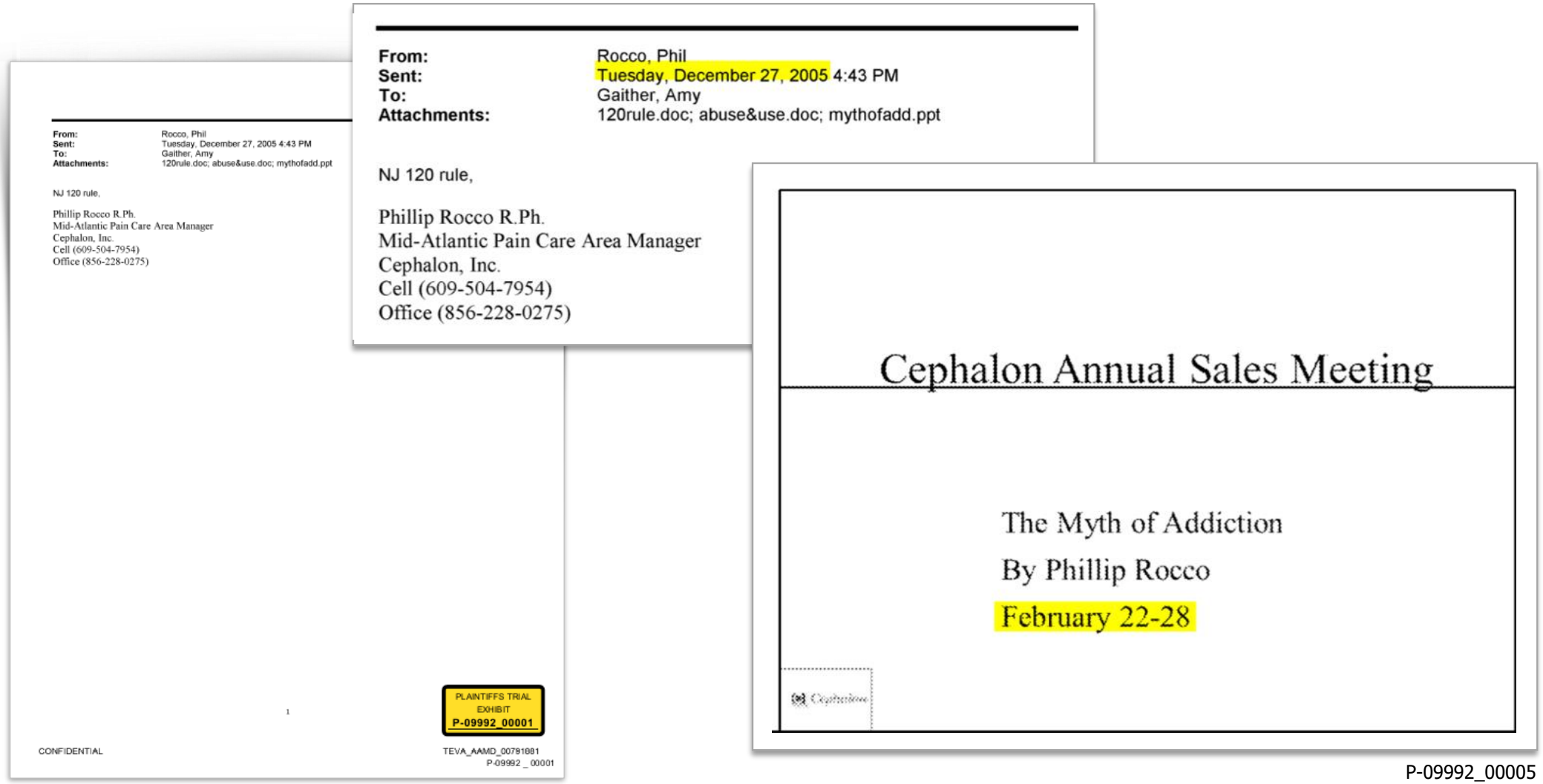
* * *

In 2002, a Cephalon annual sales meeting presentation entitled, "The Myth of Addiction" concluded there was a *"0.06% chance of becoming addicted"* and directed its sales force: "Never Refer to Addiction when talking about opioids – especially Actiq!" **P-09992_00022** (Sales representative meeting presentation).

Lemke Decl. ¶ 14

TCA Defendants Court Exhibit 00001.00020

Mid-Atlantic Region Email and Attachment (2005)



From: Rocco, Phil
Sent: Tuesday, December 27, 2005 4:43 PM
To: Gaither, Amy
Attachments: 120rule.doc; abuse&use.doc; mythofadd.ppt

NJ 120 rule,

Phillip Rocco R.Ph.
Mid-Atlantic Pain Care Area Manager
Cephalon, Inc.
Cell (609-504-7954)
Office (856-228-0275)

PLAINTIFFS TRIAL EXHIBIT P-09992_00001

CONFIDENTIAL

TEVA_AAMD_00791001
P-09992 _ 00001

P-09992_00001

Cephalon Annual Sales Meeting

The Myth of Addiction

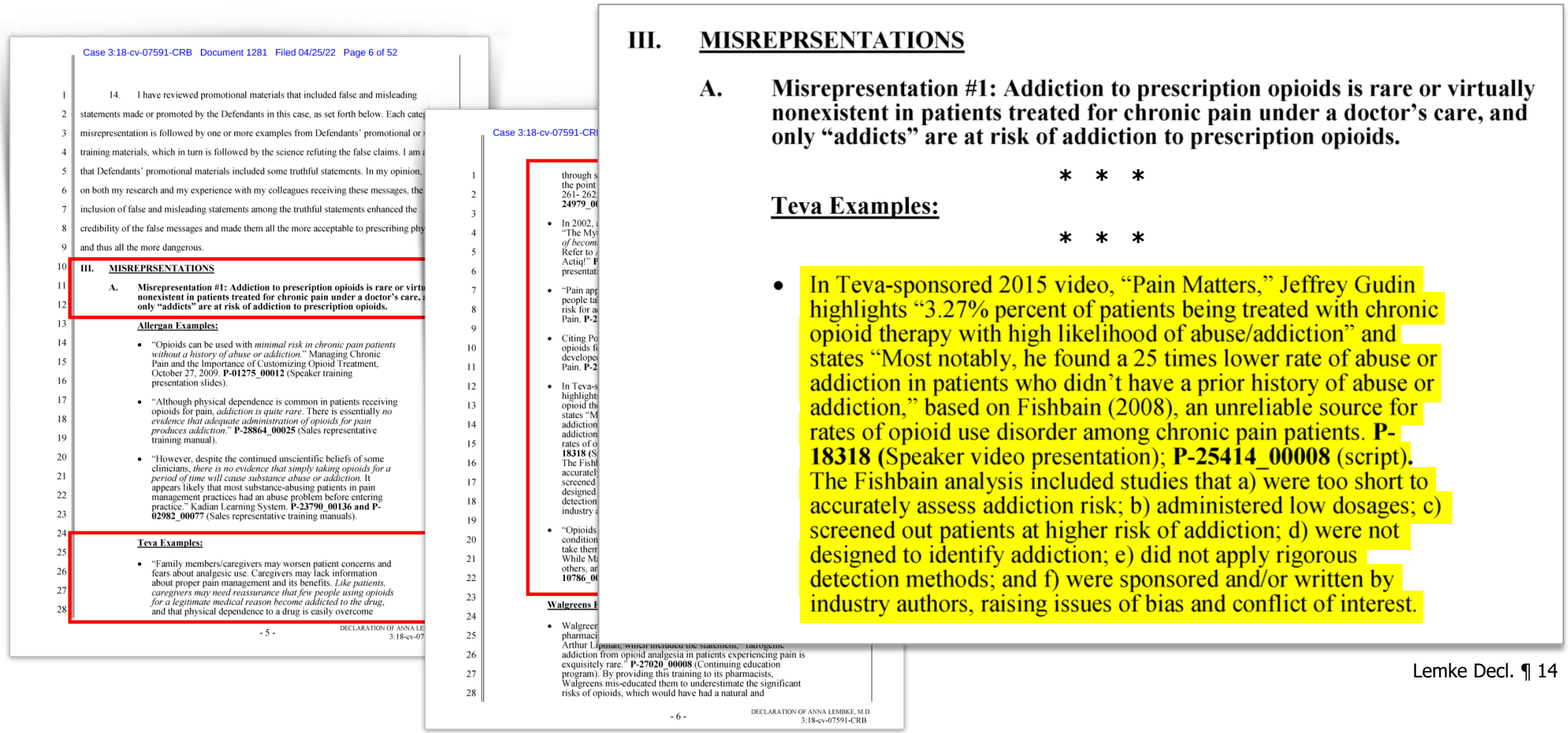
By Phillip Rocco

February 22-28

P-09992_00005

TCA Defendants Court Exhibit 00001.00021

Declaration of Anna Lembke, M.D.



Case 3:18-cv-07591-CRB Document 1281 Filed 04/25/22 Page 6 of 52

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Allergan Examples:

- "Opioids can be used with *minimal risk in chronic pain patients without a history of abuse or addiction*." Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009. **P-01275_00012** (Speaker training presentation slides).
- "Although physical dependence is common in patients receiving opioids for pain, *addiction is quite rare*. There is essentially *no evidence that adequate administration of opioids for pain produces addiction*." **P-28864_00025** (Sales representative training manual).
- "However, despite the continued unscientific beliefs of some clinicians, *there is no evidence that simply taking opioids for a period of time will cause substance abuse or addiction.* It appears likely that most substance-abusing patients in pain management practices had an abuse problem before entering practice." Kadian Learning System. **P-23790_00136 and P-02982_00077** (Sales representative training manuals).

Teva Examples:

- "Family members/caregivers may worsen patient concerns and fears about analgesic use. Caregivers may lack information about proper pain management and its benefits. *Like patients, caregivers may need reassurance that few people using opioids for a legitimate medical reason become addicted to the drug,* and that physical dependence to a drug is easily overcome

- 5 - DECLARATION OF ANNA LE 3:18-cv-07

Case 3:18-cv-07591-CR

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- In 2002, "The My *of becom* Refer to Actiq!" **P** presentati
- "Pain app people ta risk for a Pain. **P-2**
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- In Teva-s highlight opioid th states "M addiction addiction rates of o **18318** (S The Fish accurate screened designed detection industry
- "Opioids condition take them While M others, ar **10786_0**

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- 6 - DECLARATION OF ANNA LEMBKE, M.D. 3:18-cv-07591-CRB

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* * *

Teva Examples:

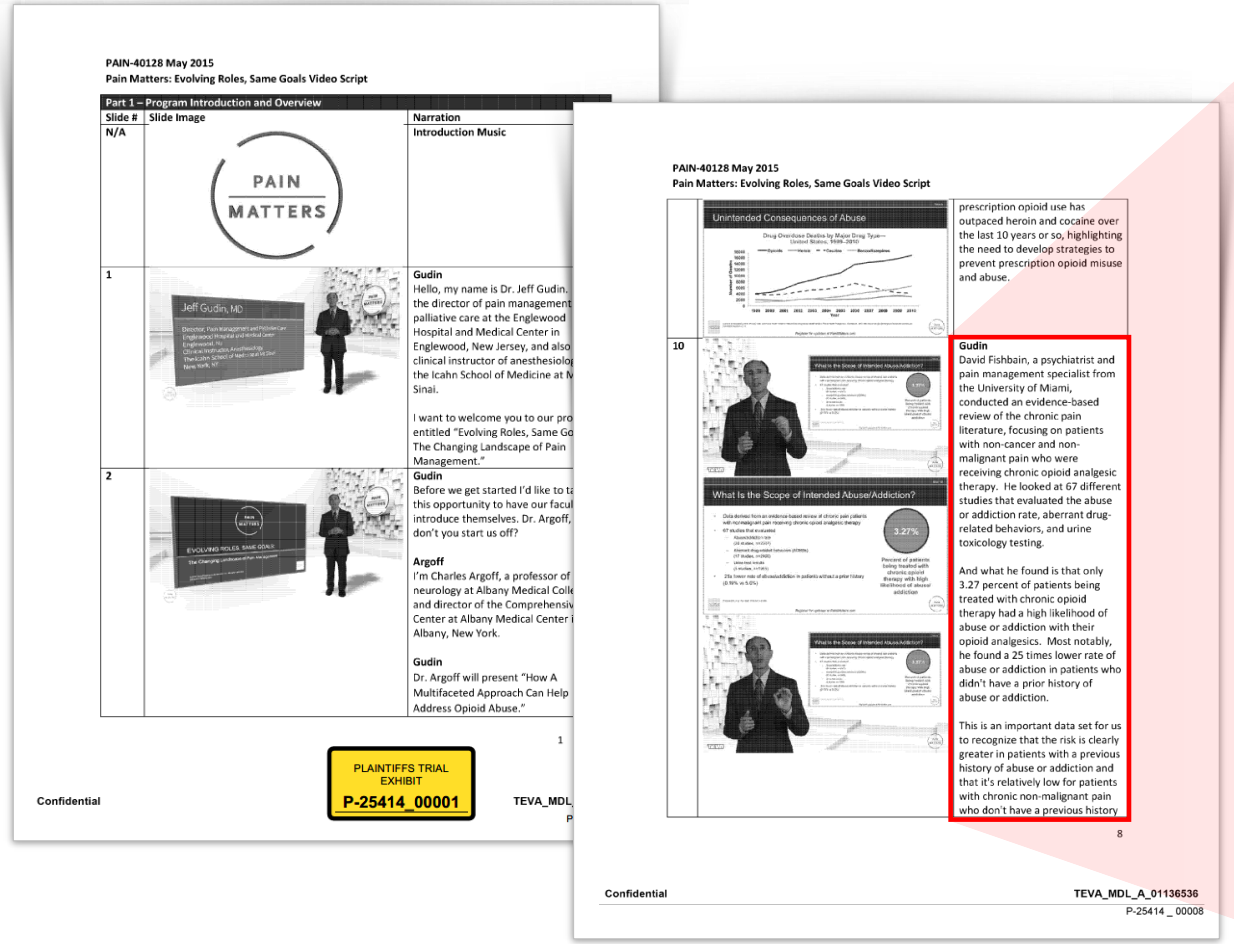
* * *

- In Teva-sponsored 2015 video, "Pain Matters," Jeffrey Gudin highlights "3.27% percent of patients being treated with chronic opioid therapy with high likelihood of abuse/addiction" and states "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," based on Fishbain (2008), an unreliable source for rates of opioid use disorder among chronic pain patients. **P-18318 (**Speaker video presentation); **P-25414_00008** (script)**.** The Fishbain analysis included studies that a) were too short to accurately assess addiction risk; b) administered low dosages; c) screened out patients at higher risk of addiction; d) were not designed to identify addiction; e) did not apply rigorous detection methods; and f) were sponsored and/or written by industry authors, raising issues of bias and conflict of interest.

Lemke Decl. ¶ 14

TCA Defendants Court Exhibit 00001.00022

Pain Matters Script (2015)



PAIN-40128 May 2015
Pain Matters: Evolving Roles, Same Goals Video Script

Part 1 – Program Introduction and Overview

Slide #	Slide Image	Narration
N/A	PAIN MATTERS	Introduction Music
1	Jeff Gudin, MD	Gudin Hello, my name is Dr. Jeff Gudin, the director of pain management palliative care at the Englewood Hospital and Medical Center in Englewood, New Jersey, and also clinical instructor of anesthesiolo the Icahn School of Medicine at M Sinai. I want to welcome you to our pro entitled "Evolving Roles, Same Go The Changing Landscape of Pain Management."
2	EVOLVING ROLES, SAME GOALS	Gudin Before we get started I'd like to ta this opportunity to have our facul introduce themselves. Dr. Argoff, don't you start us off? Argoff I'm Charles Argoff, a professor of neurology at Albany Medical Colle and director of the Comprehensiv Center at Albany Medical Center i Albany, New York. Gudin Dr. Argoff will present "How A Multifaceted Approach Can Help Address Opioid Abuse."

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PLAINTIFFS TRIAL EXHIBIT
P-25414_00001

Confidential TEVA_MDL

PAIN-40128 May 2015
Pain Matters: Evolving Roles, Same Goals Video Script

	Unintended Consequences of Abuse	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? 3.27%	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. 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

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P-25414_00008

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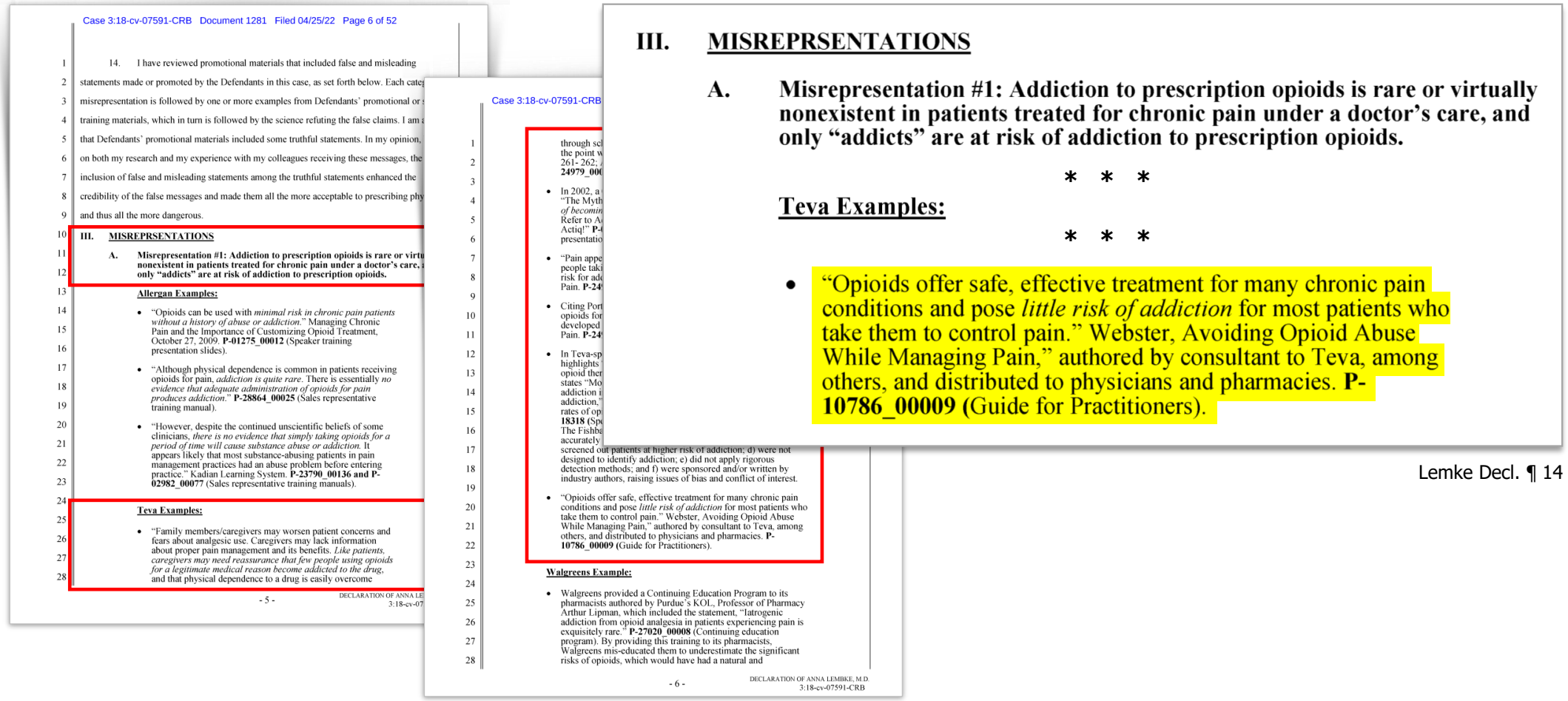
TCA Defendants Court Exhibit 00001.00023

Declaration of Anna Lembke, M.D.



Case 3:18-cv-07591-CRB Document 1281 Filed 04/25/22 Page 6 of 52

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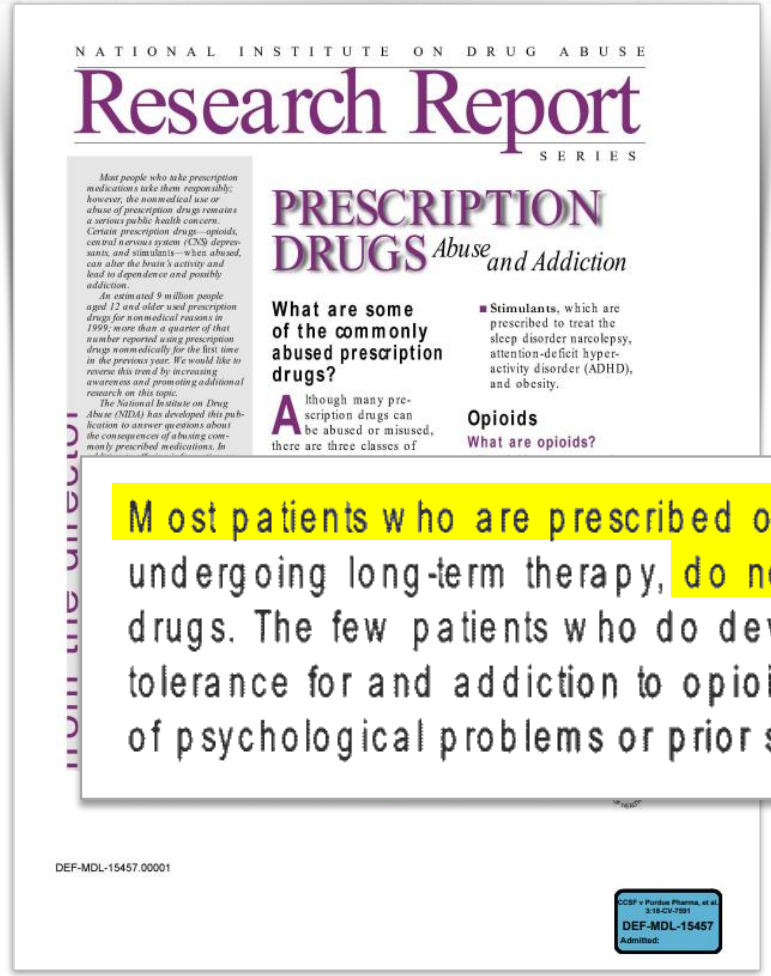
Lemke Decl. ¶ 14

TCA Defendants Court Exhibit 00001.00024

NIDA Research Report - Prescription Drugs: Abuse and Addiction (2001)



NATIONAL INSTITUTE ON DRUG ABUSE

Research Report SERIES

PRESCRIPTION DRUGS *Abuse and Addiction*

What are some of the commonly abused prescription drugs?

Although many prescription drugs can be abused or misused, there are three classes of

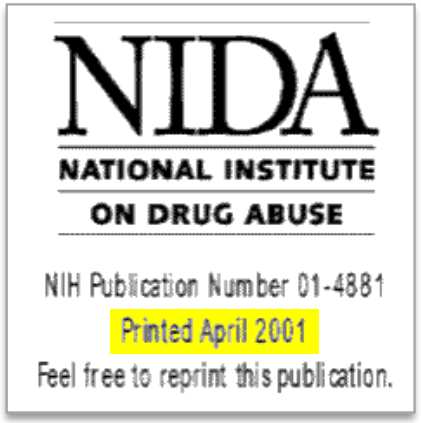
- **Stimulants**, which are prescribed to treat the sleep disorder narcolepsy, attention-deficit hyperactivity disorder (ADHD), and obesity.

Opioids

What are opioids?

DEF-MDL-15457.00001

CCSF v Purdue Pharma, et al. 3:18-CV-7591 DEF-MDL-15457 Admitted:



NIDA

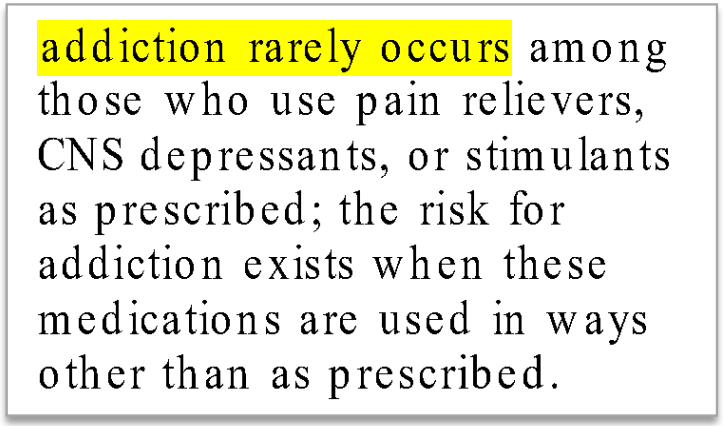
NATIONAL INSTITUTE ON DRUG ABUSE

NIH Publication Number 01-4881

Printed April 2001

Feel free to reprint this publication.

DEF-MDL-15457.00012

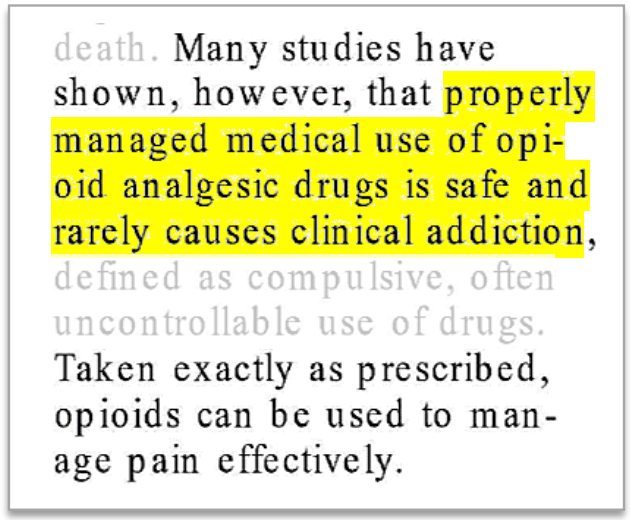


addiction rarely occurs among those who use pain relievers, CNS depressants, or stimulants as prescribed; the risk for addiction exists when these medications are used in ways other than as prescribed.

DEF-MDL-15457.00007

Most patients who are prescribed opioids for pain, even those undergoing long-term therapy, do not become addicted to the drugs. The few patients who do develop rapid and marked tolerance for and addiction to opioids usually have a history of psychological problems or prior substance abuse. In fact,

DEF-MDL-15457.00008

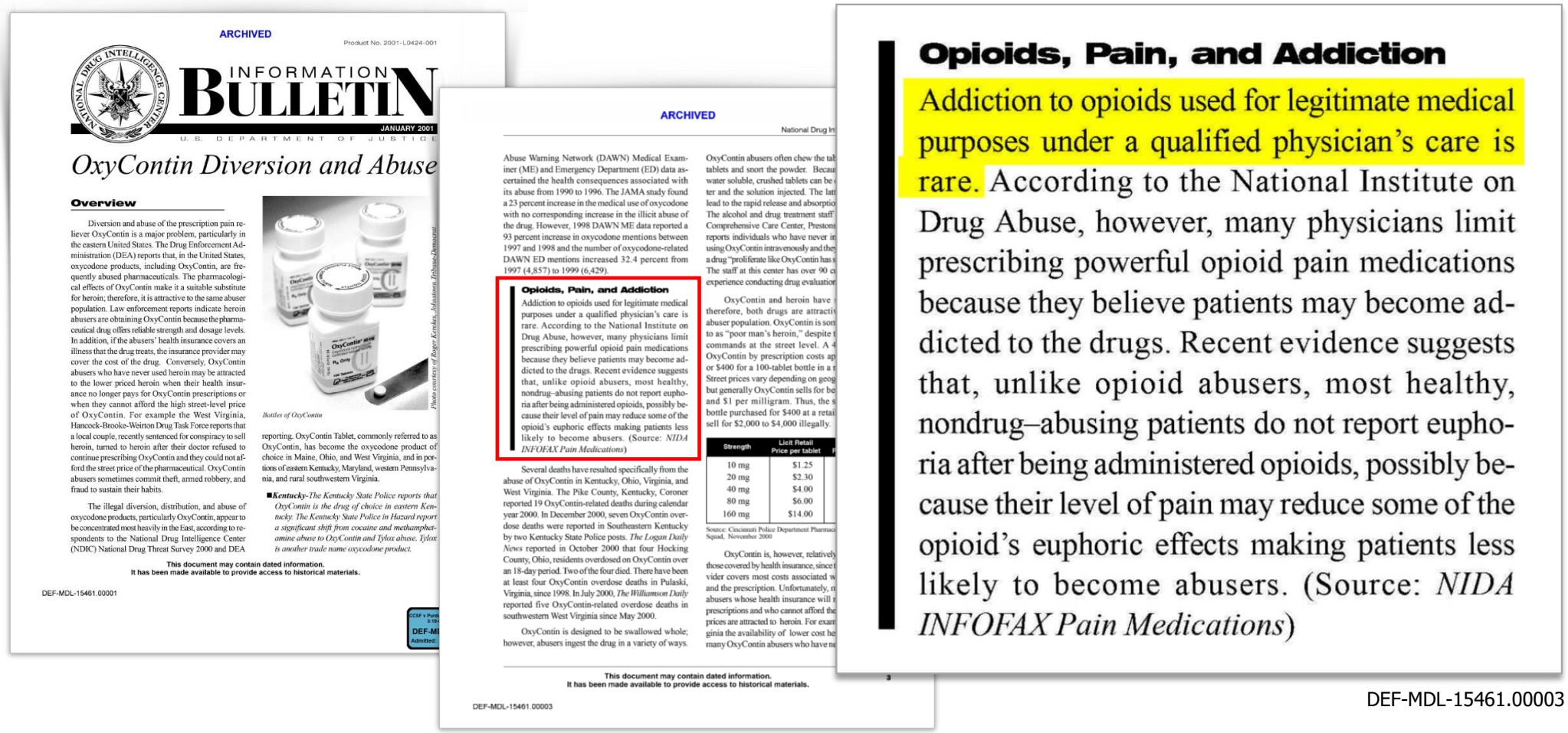


death. Many studies have shown, however, that properly managed medical use of opioid analgesic drugs is safe and rarely causes clinical addiction, defined as compulsive, often uncontrollable use of drugs. Taken exactly as prescribed, opioids can be used to manage pain effectively.

DEF-MDL-15457.00002

TCA Defendants Court Exhibit 00001.00025

DEA Information Bulletin (2001)



ARCHIVED

Product No. 2001-L0424-001

INFORMATION BULLETIN

JANUARY 2001

U.S. DEPARTMENT OF JUSTICE

OxyContin Diversion and Abuse

Overview

Diversion and abuse of the prescription pain reliever OxyContin is a major problem, particularly in the eastern United States. The Drug Enforcement Administration (DEA) reports that, in the United States, oxycodone products, including OxyContin, are frequently abused pharmaceuticals. The pharmacological effects of OxyContin make it a suitable substitute for heroin; therefore, it is attractive to the same abuser population. Law enforcement reports indicate heroin abusers are obtaining OxyContin because the pharmaceutical drug offers reliable strength and dosage levels. In addition, if the abusers' health insurance covers an illness that the drug treats, the insurance provider may cover the cost of the drug. Conversely, OxyContin abusers who have never used heroin may be attracted to the lower priced heroin when their health insurance no longer pays for OxyContin prescriptions or when they cannot afford the high street-level price of OxyContin. For example the West Virginia, Hancock-Brooke-Weirton Drug Task Force reports that a local couple, recently sentenced for conspiracy to sell heroin, turned to heroin after their doctor refused to continue prescribing OxyContin and they could not afford the street price of the pharmaceutical. OxyContin abusers sometimes commit theft, armed robbery, and fraud to sustain their habits.

The illegal diversion, distribution, and abuse of oxycodone products, particularly OxyContin, appear to be concentrated most heavily in the East, according to respondents to the National Drug Intelligence Center (NDIC) National Drug Threat Survey 2000 and DEA reporting. OxyContin Tablet, commonly referred to as OxyContin, has become the oxycodone product of choice in Maine, Ohio, and West Virginia, and in portions of eastern Kentucky, Maryland, western Pennsylvania, and rural southwestern Virginia.

Bottles of OxyContin

Photo courtesy of Roger Kershes, Johnstown Tribune-Democrat

■ ***Kentucky****-The Kentucky State Police reports that OxyContin is the drug of choice in eastern Kentucky. The Kentucky State Police in Hazard report a significant shift from cocaine and methamphetamine abuse to OxyContin and Tylox abuse. Tylox is another trade name oxycodone product.*

This document may contain dated information.
It has been made available to provide access to historical materials.

DEF-MDL-15461.00001

ARCHIVED

Abuse Warning Network (DAWN) Medical Examiner (ME) and Emergency Department (ED) data ascertained the health consequences associated with its abuse from 1990 to 1996. The JAMA study found a 23 percent increase in the medical use of oxycodone with no corresponding increase in the illicit abuse of the drug. However, 1998 DAWN ME data reported a 93 percent increase in oxycodone mentions between 1997 and 1998 and the number of oxycodone-related DAWN ED mentions increased 32.4 percent from 1997 (4,857) to 1999 (6,429).

Opioids, Pain, and Addiction

Addiction to opioids used for legitimate medical purposes under a qualified physician's care is rare. According to the National Institute on Drug Abuse, however, many physicians limit prescribing powerful opioid pain medications because they believe patients may become addicted to the drugs. Recent evidence suggests that, unlike opioid abusers, most healthy, nondrug–abusing patients do not report euphoria after being administered opioids, possibly because their level of pain may reduce some of the opioid's euphoric effects making patients less likely to become abusers. (Source: *NIDA INFOFAX Pain Medications*)

Several deaths have resulted specifically from the abuse of OxyContin in Kentucky, Ohio, Virginia, and West Virginia. The Pike County, Kentucky, Coroner reported 19 OxyContin-related deaths during calendar year 2000. In December 2000, seven OxyContin overdose deaths were reported in Southeastern Kentucky by two Kentucky State Police posts. *The Logan Daily News* reported in October 2000 that four Hocking County, Ohio, residents overdosed on OxyContin over an 18-day period. Two of the four died. There have been at least four OxyContin overdose deaths in Pulaski, Virginia, since 1998. In July 2000, *The Williamson Daily* reported five OxyContin-related overdose deaths in southwestern West Virginia since May 2000.

OxyContin is designed to be swallowed whole; however, abusers ingest the drug in a variety of ways. OxyContin abusers often chew the tablets and snort the powder. Because water soluble, crushed tablets can be ... ter and the solution injected. The latter lead to the rapid release and absorption ... The alcohol and drug treatment staff ... Comprehensive Care Center, Prestons ... reports individuals who have never ... using OxyContin intravenously and they ... a drug "proliferate like OxyContin has ... The staff at this center has over 90 ... experience conducting drug evaluation ...

OxyContin and heroin have ... therefore, both drugs are attractive ... abuser population. OxyContin is sold ... to as "poor man's heroin," despite ... commands at the street level. A 4 ... OxyContin by prescription costs ap ... or $400 for a 100-tablet bottle in a ... Street prices vary depending on geog ... but generally OxyContin sells for be ... and $1 per milligram. Thus, the ... bottle purchased for $400 at a retail ... sell for $2,000 to $4,000 illegally.

Strength	Licit Retail Price per tablet
10 mg	$1.25
20 mg	$2.30
40 mg	$4.00
80 mg	$6.00
160 mg	$14.00

Source: Cincinnati Police Department Pharmaco ... Squad, November 2000

OxyContin is, however, relatively ... those covered by health insurance, since ... vider covers most costs associated w ... and the prescription. Unfortunately, ... abusers whose health insurance will ... prescriptions and who cannot afford the ... prices are attracted to heroin. For exam ... ginia the availability of lower cost he ... many OxyContin abusers who have ne ...

This document may contain dated information.
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DEF-MDL-15461.00003

Opioids, Pain, and Addiction

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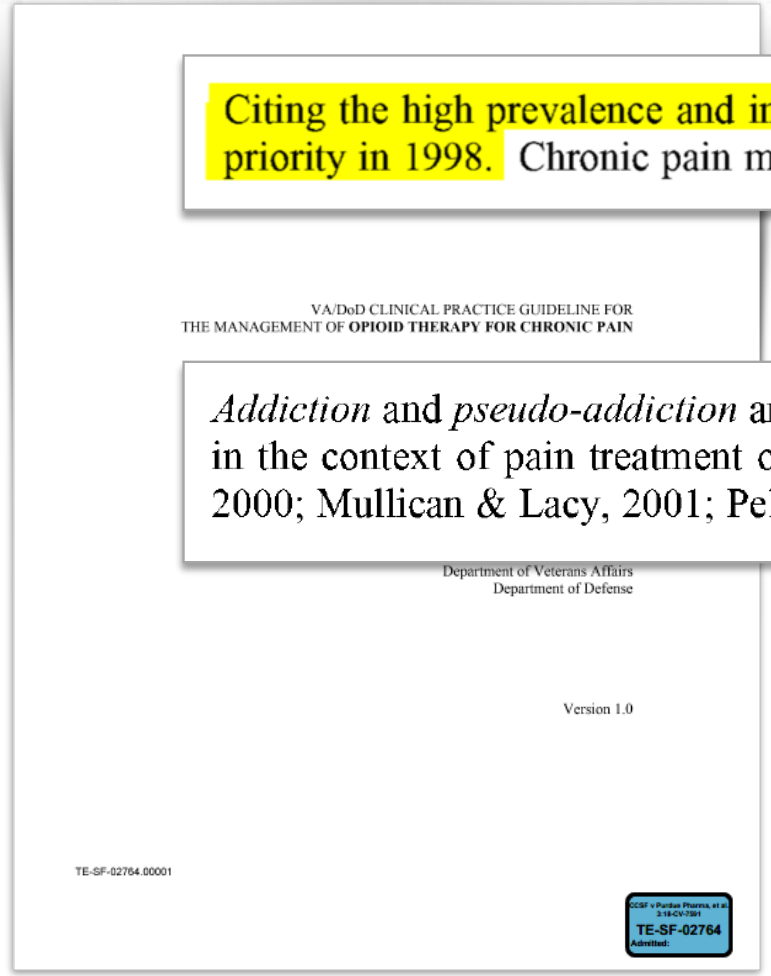
DEF-MDL-15461.00003

TCA Defendants Court Exhibit 00001.00026

VA/DoD Clinical Practice Guidelines (2003)


VA/DoD CLINICAL PRACTICE GUIDELINE FOR
THE MANAGEMENT OF **OPIOID THERAPY FOR CHRONIC PAIN**

Department of Veterans Affairs
Department of Defense

Version 1.0

TE-SF-02764.00001

TE-SF-02764
Admitted:

Citing the high prevalence and inadequate treatment of chronic pain, the VA identified pain management as a priority in 1998. Chronic pain management is a broad topic and the exact cause of pain is often multifactorial

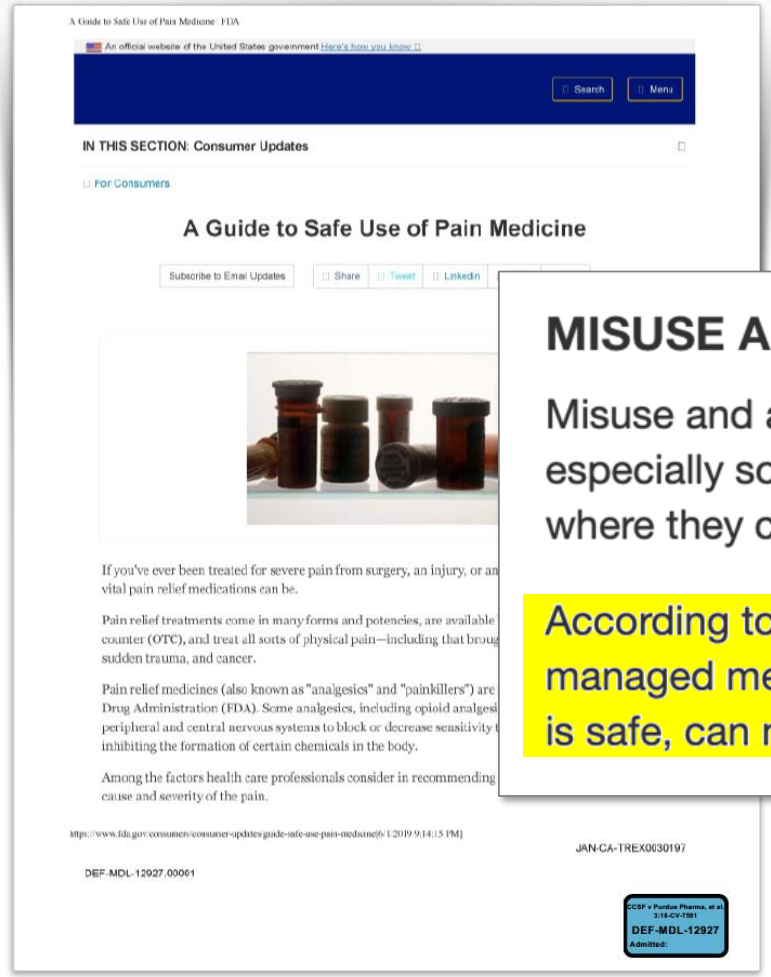
TE-SF-02764.00006

Addiction and *pseudo-addiction* are behaviors a patient may or may not develop. Repeated exposure to opioids in the context of pain treatment only rarely causes *addiction* (College of Physicians and Surgeons of Ontario, 2000; Mullican & Lacy, 2001; Peloso et al., 2000). There are a variety of biological, psychological, social, and

TE-SF-02764.00032

TCA Defendants Court Exhibit 00001.00027

FDA Website
Guide to Safe Use of Pain Medicine (2019)



MISUSE AND ABUSE

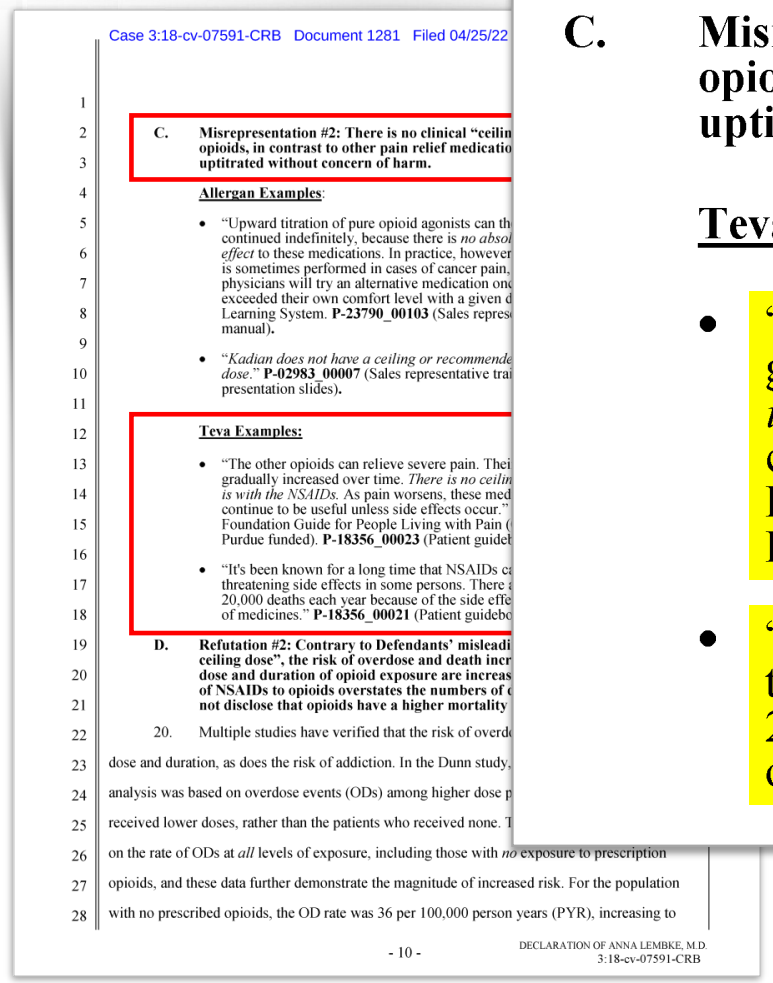
Misuse and abuse of pain medications can be extremely dangerous. This is especially so in regard to opioids. These medications should be stored in a place where they cannot be stolen.

According to the National Institutes of Health, studies have shown that properly managed medical use of opioid analgesic compounds (taken exactly as prescribed) is safe, can manage pain effectively, and rarely causes addiction.

DEF-MDL-12927.00004

TCA Defendants Court Exhibit 00001.00028

Declaration of Anna Lembke, M.D.


Case 3:18-cv-07591-CRB Document 1281 Filed 04/25/22

C. Misrepresentation #2: There is no clinical "ceilin
opioids, in contrast to other pain relief medicatio
uptitrated without concern of harm.

Allergan Examples:

- "Upward titration of pure opioid agonists can th
continued indefinitely, because there is *no absol*
effect to these medications. In practice, however
is sometimes performed in cases of cancer pain,
physicians will try an alternative medication onc
exceeded their own comfort level with a given d
Learning System. **P-23790_00103** (Sales repres
manual).

- "*Kadian does not have a ceiling or recommende*
dose." **P-02983_00007** (Sales representative trai
presentation slides).

Teva Examples:

- "The other opioids can relieve severe pain. Thei
gradually increased over time. *There is no ceilin*
is with the NSAIDs. As pain worsens, these med
continue to be useful unless side effects occur."
Foundation Guide for People Living with Pain (
Purdue funded). **P-18356_00023** (Patient guideb

- "It's been known for a long time that NSAIDs ca
threatening side effects in some persons. There a
20,000 deaths each year because of the side effe
of medicines." **P-18356_00021** (Patient guidebo

D. Refutation #2: Contrary to Defendants' misleadi
ceiling dose", the risk of overdose and death incr
dose and duration of opioid exposure are increas
of NSAIDs to opioids overstates the numbers of
not disclose that opioids have a higher mortality

20. Multiple studies have verified that the risk of overd
dose and duration, as does the risk of addiction. In the Dunn study,
analysis was based on overdose events (ODs) among higher dose p
received lower doses, rather than the patients who received none. T
on the rate of ODs at *all* levels of exposure, including those with *no* exposure to prescription
opioids, and these data further demonstrate the magnitude of increased risk. For the population
with no prescribed opioids, the OD rate was 36 per 100,000 person years (PYR), increasing to

- 10 -

DECLARATION OF ANNA LEMBKE, M.D.
3:18-cv-07591-CRB

C. Misrepresentation #2: There is no clinical "ceiling dose" of prescription opioids, in contrast to other pain relief medications, so opioids can be uptitrated without concern of harm.

* * *

Teva Examples:

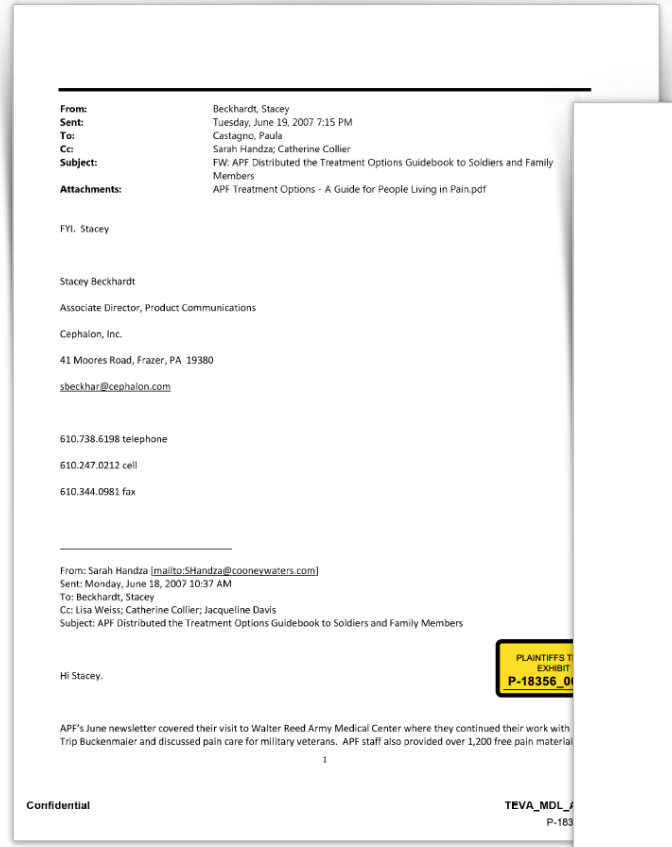
- "The other opioids can relieve severe pain. Their doses can be gradually increased over time. *There is no ceiling dose as there is with the NSAIDs.* As pain worsens, these medications continue to be useful unless side effects occur." American Pain Foundation Guide for People Living with Pain (Cephalon and Purdue funded). **P-18356_00023** (Patient guidebook).

- "It's been known for a long time that NSAIDs can cause life-threatening side effects in some persons. There are 10,000 to 20,000 deaths each year because of the side effects of this class of medicines." **P-18356_00021** (Patient guidebook).

Lemke Decl. ¶ 19

TCA Defendants Court Exhibit 00001.00029

Treatment Options: A Guide For People Living With Pain
American Pain Foundation (2007)



From: Beckhardt, Stacey
Sent: Tuesday, June 19, 2007 7:15 PM
To: Castagno, Paula
Cc: Sarah Handza; Catherine Collier
Subject: FW: APF Distributed the Treatment Options Guidebook to Soldiers and Family Members
Attachments: APF Treatment Options - A Guide for People Living in Pain.pdf

FYI. Stacey

Stacey Beckhardt

Associate Director, Product Communications

Cephalon, Inc.

41 Moores Road, Frazer, PA 19380

sbeckhar@cephalon.com

610.738.6198 telephone

610.247.0212 cell

610.344.0981 fax

From: Sarah Handza [mailto:SHandza@cooneywaters.com]
Sent: Monday, June 18, 2007 10:37 AM
To: Beckhardt, Stacey
Cc: Lisa Weiss; Catherine Collier; Jacqueline Davis
Subject: APF Distributed the Treatment Options Guidebook to Soldiers and Family Members

PLAINTIFFS T
EXHIBIT
P-18356_0

Hi Stacey.

APF's June newsletter covered their visit to Walter Reed Army Medical Center where they continued their work with Trip Buckenmaier and discussed pain care for military veterans. APF staff also provided over 1,200 free pain material

1

Confidential

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P-183

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Confidential

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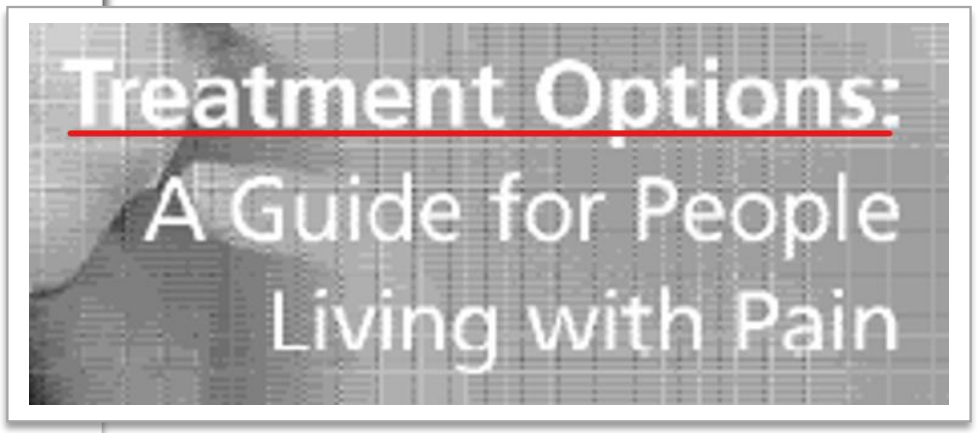
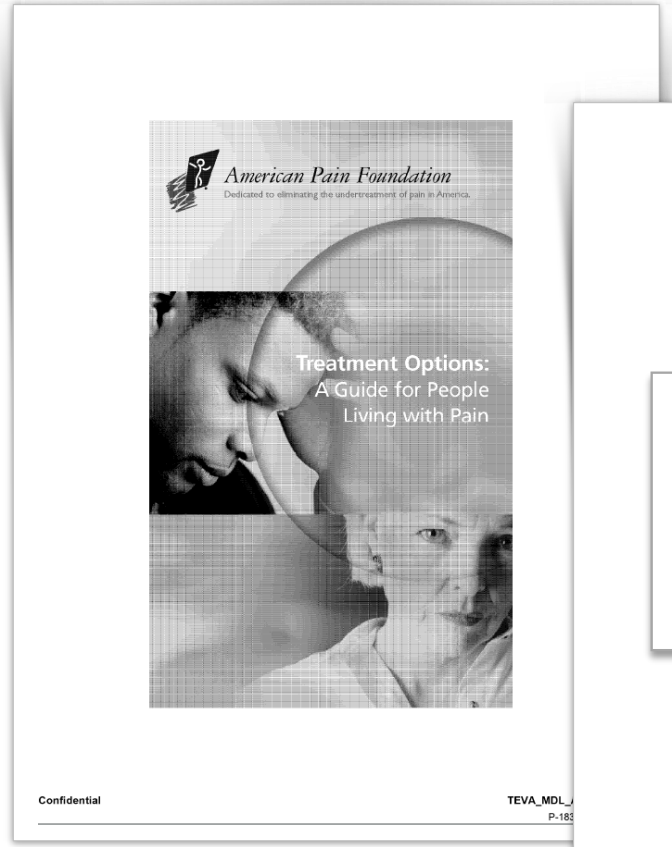
P-18356_00004

P-18356_00004



TCA Defendants Court Exhibit 00001.00030

Treatment Options: A Guide For People Living With Pain American Pain Foundation (2007)



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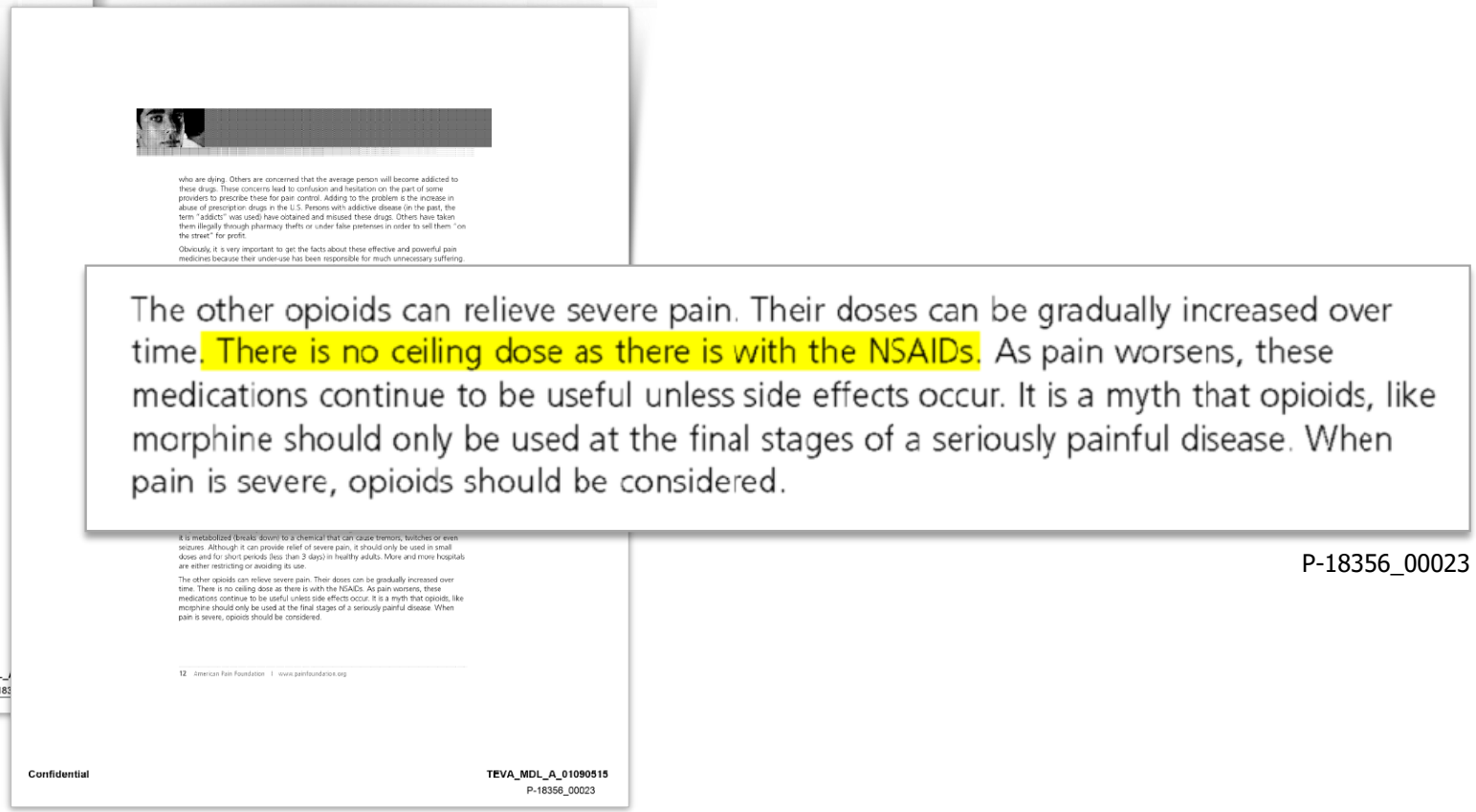
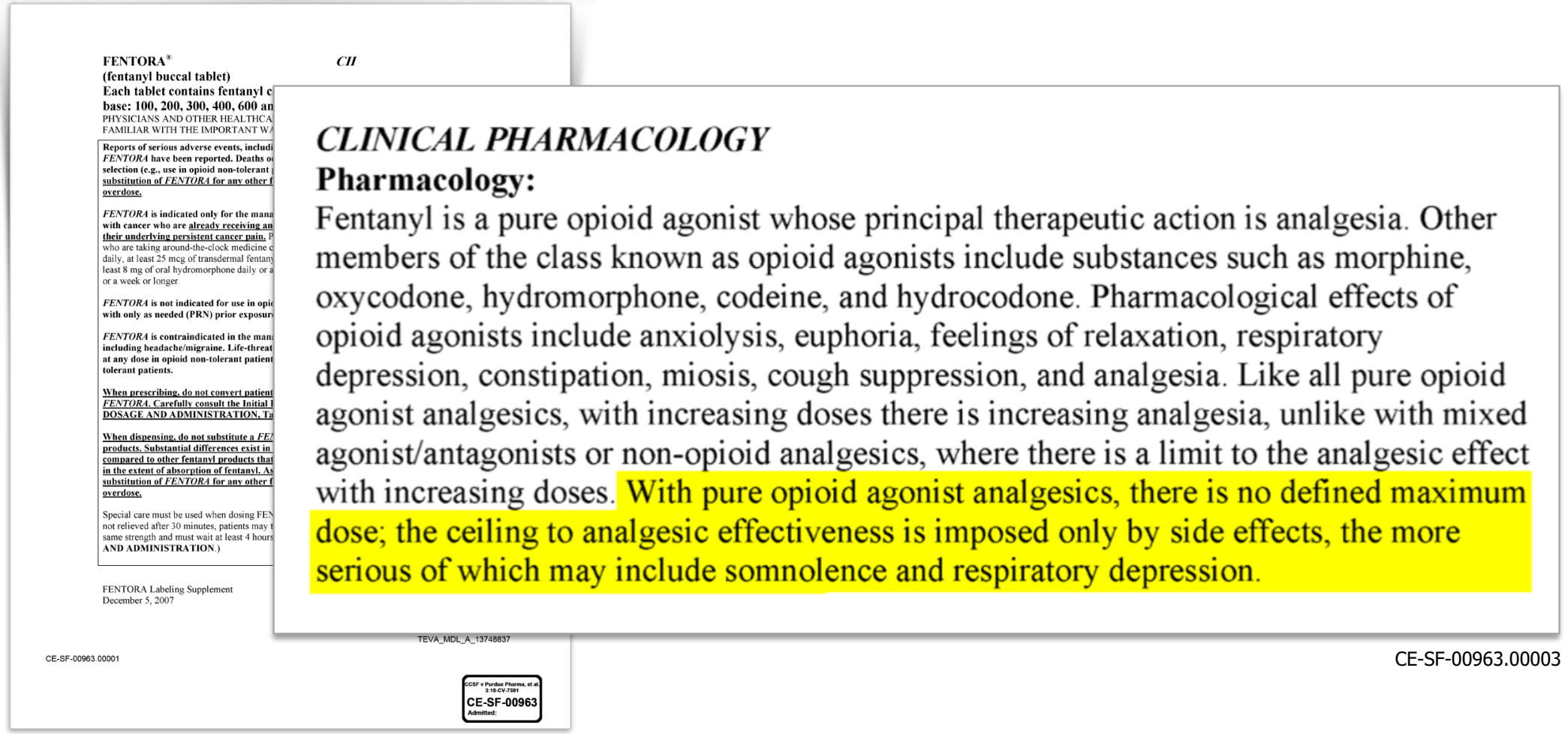


The other opioids can relieve severe pain. Their doses can be gradually increased over time. There is no ceiling dose as there is with the NSAIDs. As pain worsens, these medications continue to be useful unless side effects occur. It is a myth that opioids, like morphine should only be used at the final stages of a seriously painful disease. When pain is severe, opioids should be considered.

P-18356_00023

TCA Defendants Court Exhibit 00001.00031

Fentora FDA Approved Label (2007)



FENTORA®
(fentanyl buccal tablet)
Each tablet contains fentanyl c
base: 100, 200, 300, 400, 600 an
PHYSICIANS AND OTHER HEALTHCA
FAMILIAR WITH THE IMPORTANT WA

Reports of serious adverse events, includi
***FENTORA* have been reported. Deaths o**
selection (e.g., use in opioid non-tolerant
substitution of *FENTORA* for any other f
overdose.

***FENTORA* is indicated only for the mana**
with cancer who are already receiving an
their underlying persistent cancer pain. P
who are taking around-the-clock medicine c
daily, at least 25 mcg of transdermal fentany
least 8 mg of oral hydromorphone daily or a
or a week or longer.

***FENTORA* is not indicated for use in opi**
with only as needed (PRN) prior exposur

***FENTORA* is contraindicated in the man**
including headache/migraine. Life-threat
at any dose in opioid non-tolerant patient
tolerant patients.

When prescribing, do not convert patient
***FENTORA*. Carefully consult the Initial**
DOSAGE AND ADMINISTRATION, Ta

When dispensing, do not substitute a *FE*
products. Substantial differences exist in
compared to other fentanyl products that
in the extent of absorption of fentanyl. As
substitution of *FENTORA* for any other f
overdose.

Special care must be used when dosing FEN
not relieved after 30 minutes, patients may t
same strength and must wait at least 4 hours
AND ADMINISTRATION.)

FENTORA Labeling Supplement
December 5, 2007

CE-SF-00963.00001

CII

CLINICAL PHARMACOLOGY

Pharmacology:

Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

TEVA_MDL_A_13748837

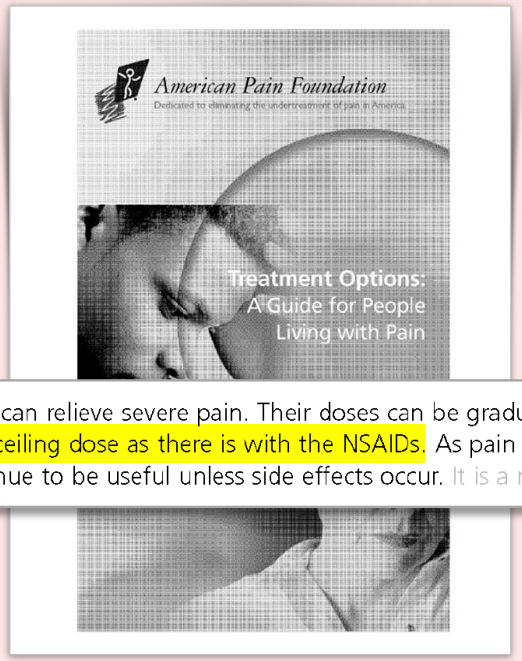
CCSF v Purdue Pharma, et al.
3:18-CV-7591
CE-SF-00963
Admitted:

CE-SF-00963.00003

TCA Defendants Court Exhibit 00001.00032

Treatment Options & Fentora FDA Approved Label

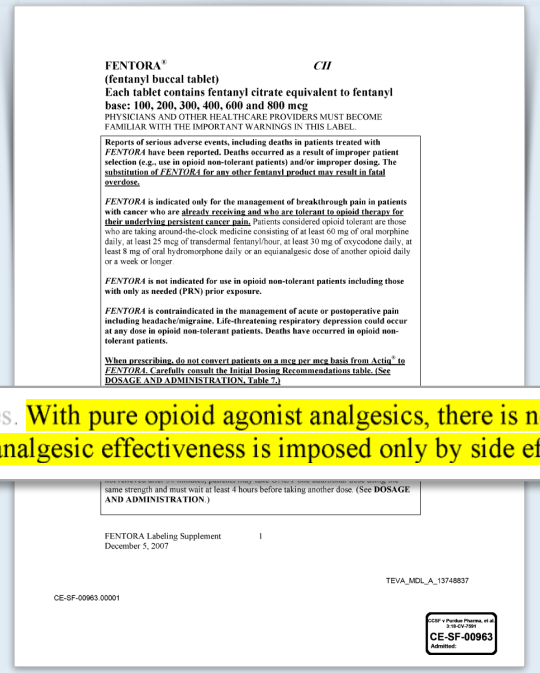
Treatment Options (2007)



The other opioids can relieve severe pain. Their doses can be gradually increased over time. There is no ceiling dose as there is with the NSAIDs. As pain worsens, these medications continue to be useful unless side effects occur. It is a myth that opioids, like

P-18356_00023

Fentora FDA Label (2007)



FENTORA® *CII*
(fentanyl buccal tablet)
Each tablet contains fentanyl citrate equivalent to fentanyl base: 100, 200, 300, 400, 600 and 800 mcg
PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

Reports of serious adverse events, including deaths in patients treated with *FENTORA* have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of *FENTORA* for any other fentanyl product may result in fatal overdose.

***FENTORA* is indicated only for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily or a week or longer

***FENTORA* is not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure.**

***FENTORA* is contraindicated in the management of acute or postoperative pain including headache/migraine. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients.**

When prescribing, do not convert patients on a mcg per mcg basis from Actiq® to *FENTORA*. Carefully consult the Initial Dosing Recommendations table. (See DOSAGE AND ADMINISTRATION, Table 7.)

same strength and must wait at least 4 hours before taking another dose. (See **DOSAGE AND ADMINISTRATION**.)

FENTORA Labeling Supplement 1
December 5, 2007

TEVA_MDL_A_13748837

CE-SF-00963.00001

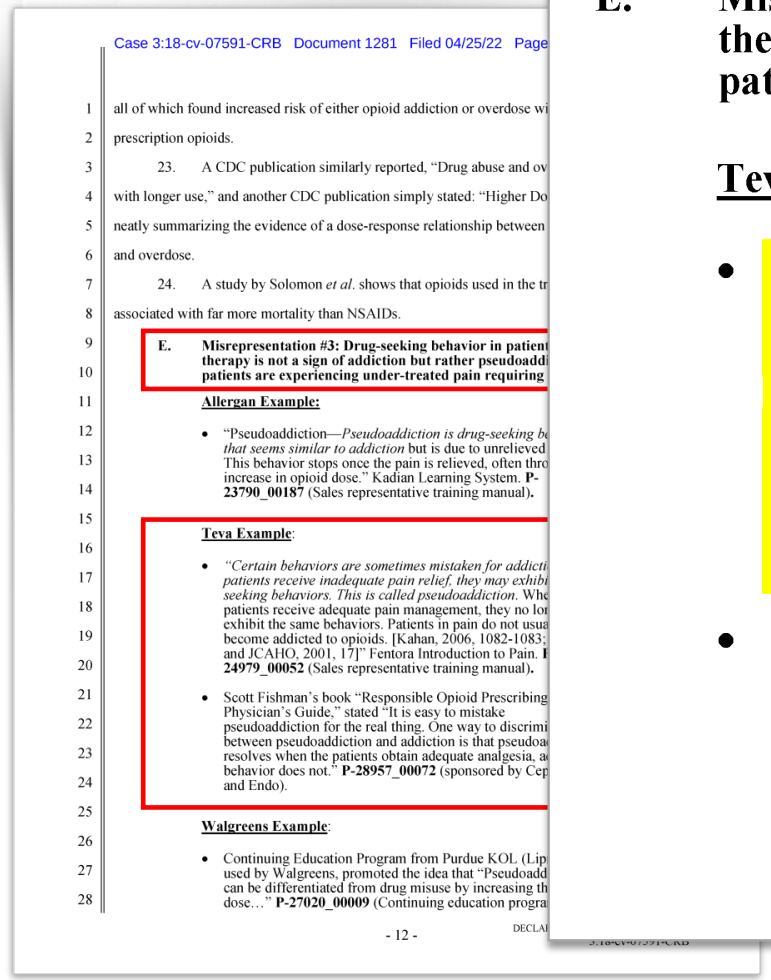
CE-SF-00963
Admitted:

with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more

CE-SF-00963.00003

TCA Defendants Court Exhibit 00001.00033

Declaration of Anna Lembke, M.D.



Case 3:18-cv-07591-CRB Document 1281 Filed 04/25/22 Page

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prescription opioids.

23. A CDC publication similarly reported, "Drug abuse and ov
with longer use," and another CDC publication simply stated: "Higher Do
neatly summarizing the evidence of a dose-response relationship between
and overdose.

24. A study by Solomon *et al.* shows that opioids used in the tr
associated with far more mortality than NSAIDs.

E. Misrepresentation #3: Drug-seeking behavior in patient therapy is not a sign of addiction but rather pseudoaddi patients are experiencing under-treated pain requiring

Allergan Example:

- "Pseudoaddiction—*Pseudoaddiction is drug-seeking be that seems similar to addiction* but is due to unrelieved This behavior stops once the pain is relieved, often thro increase in opioid dose." Kadian Learning System. **P-23790_00187** (Sales representative training manual).

Teva Example:

- *"Certain behaviors are sometimes mistaken for addicti patients receive inadequate pain relief, they may exhibi seeking behaviors. This is called pseudoaddiction.* Whe patients receive adequate pain management, they no lo exhibit the same behaviors. Patients in pain do not usua become addicted to opioids. [Kahan, 2006, 1082-1083; and JCAHO, 2001, 17]" Fentora Introduction to Pain. **P-24979_00052** (Sales representative training manual).
- Scott Fishman's book "Responsible Opioid Prescribing Physician's Guide," stated "It is easy to mistake pseudoaddiction for the real thing. One way to discrimi between pseudoaddiction and addiction is that pseudoa resolves when the patients obtain adequate analgesia, a behavior does not." **P-28957_00072** (sponsored by Cep and Endo).

Walgreens Example:

- Continuing Education Program from Purdue KOL (Lip used by Walgreens, promoted the idea that "Pseudoadd can be differentiated from drug misuse by increasing th dose…" **P-27020_00009** (Continuing education progra

- 12 -

DECLAI

E. Misrepresentation #3: Drug-seeking behavior in patients receiving opioid therapy is not a sign of addiction but rather pseudoaddiction, and these patients are experiencing under-treated pain requiring more opioids.

* * *

Teva Example:

- *"Certain behaviors are sometimes mistaken for addiction. If patients receive inadequate pain relief, they may exhibit drug-seeking behaviors. This is called pseudoaddiction*. When these patients receive adequate pain management, they no longer exhibit the same behaviors. Patients in pain do not usually become addicted to opioids. [Kahan, 2006, 1082-1083; NPC and JCAHO, 2001, 17]" Fentora Introduction to Pain. **P-24979_00052** (Sales representative training manual).
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Lemke Decl. ¶ 24

California Health & Safety Code § 11156

Effective: January 1, 2007

West's Ann.Cal.Health & Safety Code § 11156

§ 11156. Prescribing, administering or dispensing controlled substances to addict prohibited; exceptions; "addict" defined

Currentness

(a) Except as provided in Section 2241 of the Business and Professions Code, no person shall prescribe for, or administer, or dispense a controlled substance to, an addict, or to any person representing himself or herself as such, except as permitted by this division.

(b)(1) For purposes of this section, "addict" means a person whose actions are characterized by craving in combination with one or more of the following:

(A) Impaired control over drug use.

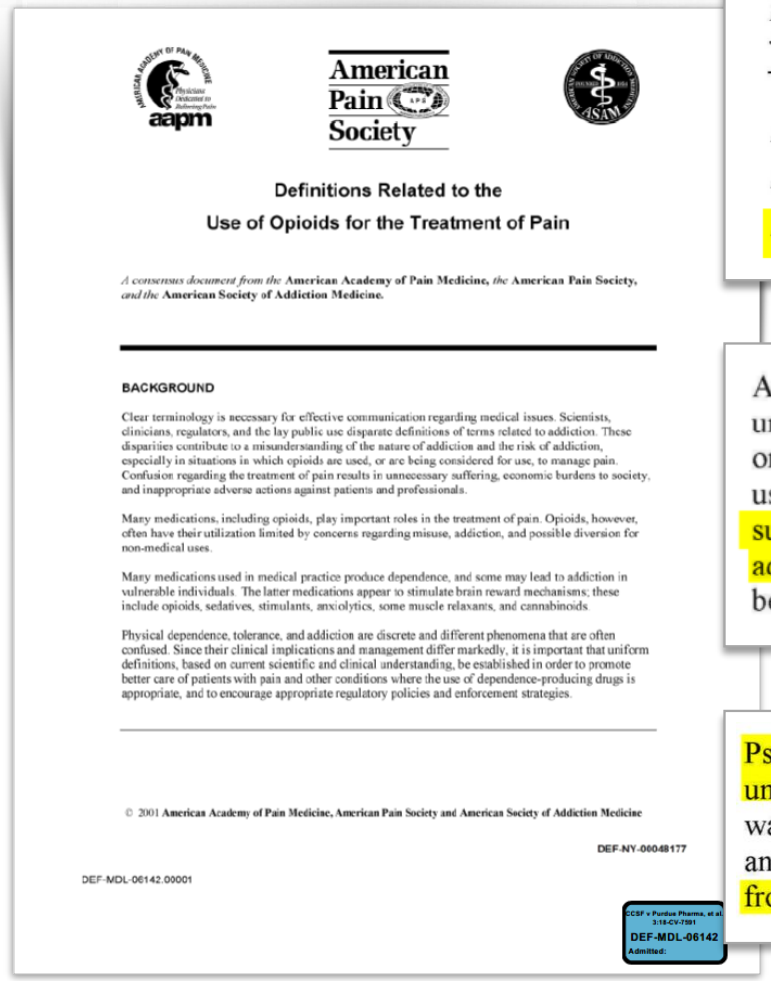
(B) Compulsive use.

(C) Continued use despite harm.

(2) Notwithstanding paragraph (1), a person whose drug-seeking behavior is primarily due to the inadequate control of pain is not an addict within the meaning of this section.

TCA Defendants Court Exhibit 00001.00035

American Society of Addiction Medicine (ASAM) (2001)



American Pain Society

Definitions Related to the
Use of Opioids for the Treatment of Pain

A consensus document from the **American Academy of Pain Medicine,** *the* **American Pain Society,** *and the* **American Society of Addiction Medicine.**

BACKGROUND

Clear terminology is necessary for effective communication regarding medical issues. Scientists, clinicians, regulators, and the lay public use disparate definitions of terms related to addiction. These disparities contribute to a misunderstanding of the nature of addiction and the risk of addiction, especially in situations in which opioids are used, or are being considered for use, to manage pain. Confusion regarding the treatment of pain results in unnecessary suffering, economic burdens to society, and inappropriate adverse actions against patients and professionals.

Many medications, including opioids, play important roles in the treatment of pain. Opioids, however, often have their utilization limited by concerns regarding misuse, addiction, and possible diversion for non-medical uses.

Many medications used in medical practice produce dependence, and some may lead to addiction in vulnerable individuals. The latter medications appear to stimulate brain reward mechanisms; these include opioids, sedatives, stimulants, anxiolytics, some muscle relaxants, and cannabinoids.

Physical dependence, tolerance, and addiction are discrete and different phenomena that are often confused. Since their clinical implications and management differ markedly, it is important that uniform definitions, based on current scientific and clinical understanding, be established in order to promote better care of patients with pain and other conditions where the use of dependence-producing drugs is appropriate, and to encourage appropriate regulatory policies and enforcement strategies.

This document was prepared by the following committee members: Seddon Savage, MD (Chair) - APS; Edward C. Covington, MD - AAPM; Howard A. Heit, MD - ASAM; John Hunt, MD - AAPM; David Joranson, MSSW - APS; and Sidney H. Schnoll, MD, PhD - ASAM.

Approved by the AAPM Board of Directors on February 13, 2001

Approved by the APS Board of Directors on February 14, 2001

Approved by the ASAM Board of Directors on February 21, 2001

DEF-MDL-06142.00004

Addiction in the course of opioid therapy of pain can best be assessed after the pain has been brought under adequate control, though this is not always possible. Addiction is recognized by the observation of one or more of its characteristic features: impaired control, craving and compulsive use, and continued use despite negative physical, mental, and/or social consequences. An individual's behaviors that may suggest addiction sometimes are simply a reflection of unrelieved pain or other problems unrelated to addiction. Therefore, good clinical judgment must be used in determining whether the pattern of behaviors signals the presence of addiction or reflects a different issue.

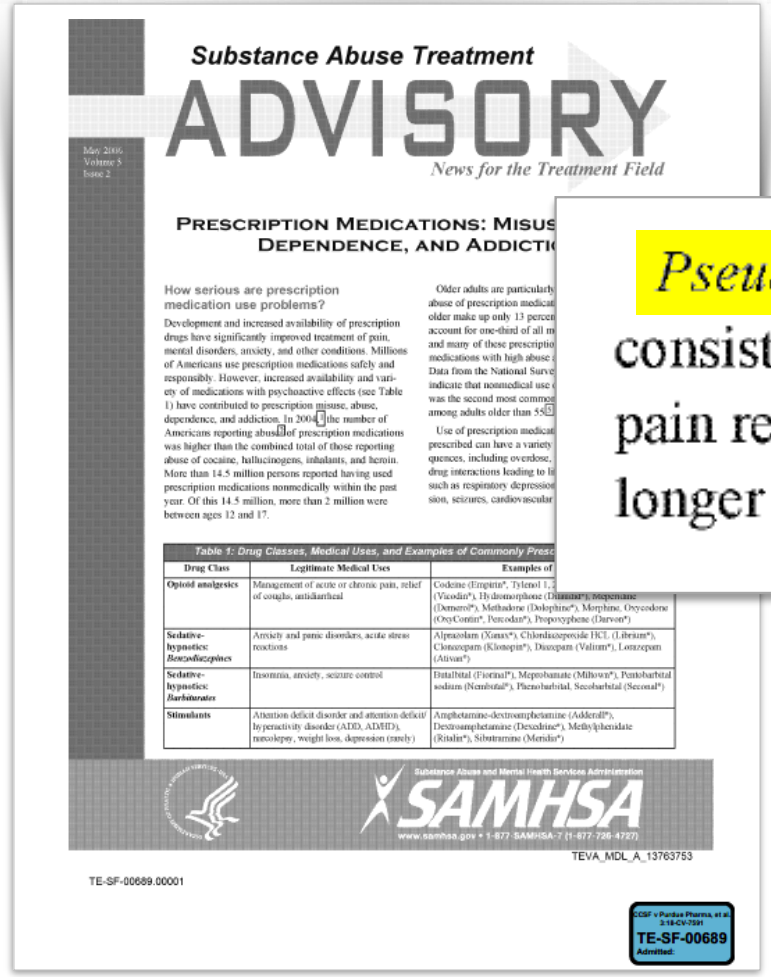
DEF-MDL-06142.00002

Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may "clock watch," and may otherwise seem inappropriately "drug seeking." Even such behaviors as illicit drug use and deception can occur in the patient's efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when pain is effectively treated

DEF-MDL-06142.00003

TCA Defendants Court Exhibit 00001.00036

Substance Abuse and Mental Health Services Administration (SAMHSA) (2008)



Substance Abuse Treatment

ADVISORY

News for the Treatment Field

May 2006
Volume 5
Issue 2

PRESCRIPTION MEDICATIONS: MISUS
DEPENDENCE, AND ADDICTI

How serious are prescription medication use problems?

Development and increased availability of prescription drugs have significantly improved treatment of pain, mental disorders, anxiety, and other conditions. Millions of Americans use prescription medications safely and responsibly. However, increased availability and variety of medications with psychoactive effects (see Table 1) have contributed to prescription misuse, abuse, dependence, and addiction. In 2004, the number of Americans reporting abuse of prescription medications was higher than the combined total of those reporting abuse of cocaine, hallucinogens, inhalants, and heroin. More than 14.5 million persons reported having used prescription medications nonmedically within the past year. Of this 14.5 million, more than 2 million were between ages 12 and 17.

Older adults are particularly
abuse of prescription medicat
older make up only 13 percen
account for one-third of all m
and many of these prescriptio
medications with high abuse
Data from the National Surve
indicate that nonmedical use
was the second most commo
among adults older than 55

Use of prescription medicat
prescribed can have a variety
quences, including overdose,
drug interactions leading to li
such as respiratory depressio
sion, seizures, cardiovascular

Table 1: Drug Classes, Medical Uses, and Examples of Commonly Presc

Drug Class	Legitimate Medical Uses	Examples of
Opioid analgesics	Management of acute or chronic pain, relief of coughs, antidiarrheal	Codeine (Empirin®, Tylenol 1, 2, 3), Hydromorphone (Dilaudid®), Hydrocodone (Vicodin®), Meperidine (Demerol®), Methadone (Dolophine®), Morphine, Oxycodone (OxyContin®, Percodan®), Propoxyphene (Darvon®)
Sedative-hypnotics: *Benzodiazepines*	Anxiety and panic disorders, acute stress reactions	Alprazolam (Xanax®), Chlordiazepoxide HCl, (Librium®), Clonazepam (Klonopin®), Diazepam (Valium®), Lorazepam (Ativan®)
Sedative-hypnotics: *Barbiturates*	Insomnia, anxiety, seizure control	Butalbital (Fiorinal®), Meprobamate (Miltown®), Pentobarbital sodium (Nembutal®), Phenobarbital, Secobarbital (Seconal®)
Stimulants	Attention deficit disorder and attention deficit/ hyperactivity disorder (ADD, ADHD), narcolepsy, weight loss, depression (rarely)	Amphetamine-dextroamphetamine (Adderall®), Dextroamphetamine (Dexedrine®), Methylphenidate (Ritalin®), Sibutramine (Meridia®)

Substance Abuse and Mental Health Services Administration
SAMHSA
www.samhsa.gov • 1-877-SAMHSA-7 (1-877-726-4727)

TEVA_MDL_A_13763753

TE-SF-00689.00001

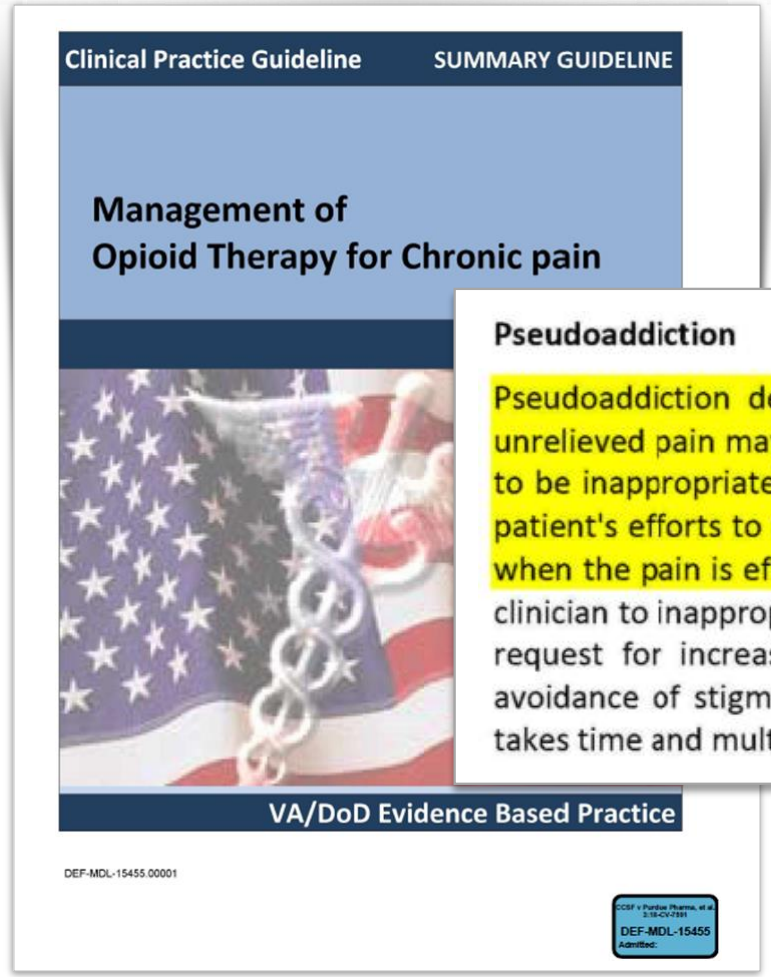
CCSF v Purdue Pharma, et al.
3:18-CV-7591
TE-SF-00689
Admitted:

Pseudoaddiction: Drug-seeking and other behavior that is consistent with addiction but actually results from inadequate pain relief. Once the pain is adequately treated, the person no longer abuses the medication[8]

TE-SF-00689.00002

TCA Defendants Court Exhibit 00001.00037

VA/DoD Clinical Practice Guidelines (2010)



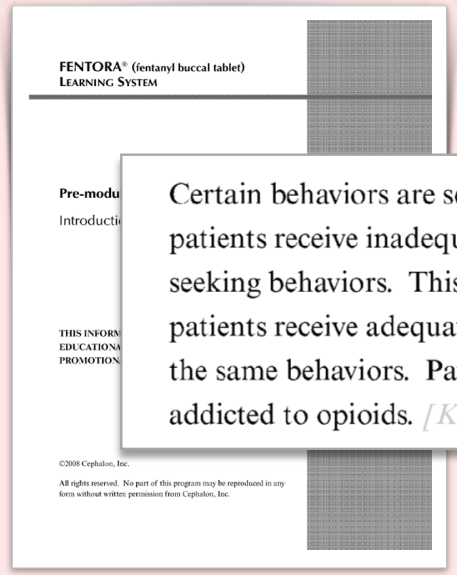
Pseudoaddiction

Pseudoaddiction describes patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may "clock watch," and may otherwise seem to be inappropriately "drug seeking." Even such behaviors as illicit drug use and deception can occur in the patient's efforts to obtain pain relief. In contrast to true addiction, in pseudoaddiction the behaviors resolve when the pain is effectively treated (Definitions, 2001). Misunderstanding of this phenomenon may lead the clinician to inappropriately stigmatize the patient with the label 'addict.' In the setting of unrelieved pain, the request for increases in drug dose requires careful assessment, renewed efforts to manage pain, and avoidance of stigmatizing labels. Distinguishing addiction from pseudoaddiction can be difficult and often takes time and multiple patient encounters.

DEF-MDL-15455.00014

TCA Defendants Court Exhibit 00001.00038

Fentora Learning System & SAMHSA, VA/DoD, ASAM


FENTORA® (fentanyl buccal tablet)
LEARNING SYSTEM

Pre-modu
Introducti

THIS INFORM
EDUCATIONA
PROMOTION

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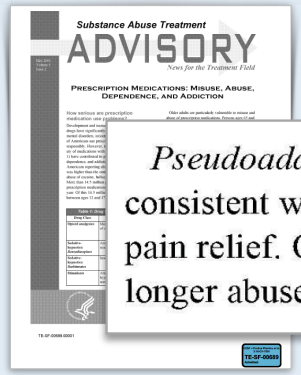
2008 Fentora Learning System

Certain behaviors are sometimes mistaken for addiction. If patients receive inadequate pain relief, they may exhibit drug-seeking behaviors. This is called pseudoaddiction. When these patients receive adequate pain management, they no longer exhibit the same behaviors. Patients in pain do not usually become addicted to opioids. *[Kahan, 2006, 1082–1083; NPC and JCAHO,*

P-24979_00052


Substance Abuse Treatment
ADVISORY
News for the Treatment Field
PRESCRIPTION MEDICATIONS: MISUSE, ABUSE, DEPENDENCE, AND ADDICTION

2008 SAMHSA

Pseudoaddiction: Drug-seeking and other behavior that is consistent with addiction but actually results from inadequate pain relief. Once the pain is adequately treated, the person no longer abuses the medication.[8]

TE-SF-00689.00002

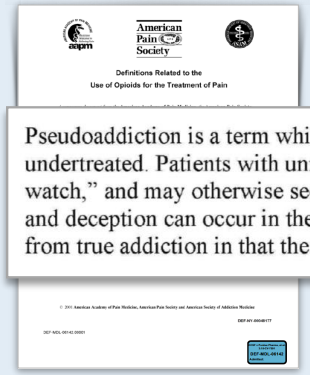

Clinical Practice Guideline SUMMARY GUIDELINE
Management of
Opioid Therapy for Chronic pain
May, 2010

2010 VA/DoD

Pseudoaddiction

Pseudoaddiction describes patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may "clock watch," and may otherwise seem to be inappropriately "drug seeking." Even such behaviors as illicit drug use and deception can occur in the patient's efforts to obtain pain relief. In contrast to true addiction, in pseudoaddiction the behaviors resolve when the pain is effectively treated (Definitions, 2001). Misunderstanding of this phenomenon may lead the clinician to inappropriately stigmatize the patient with the label 'addict.' In the setting of unrelieved pain, the request for increases in drug dose requires careful assessment, renewed efforts to manage pain, and avoidance of stigmatizing labels. Distinguishing addiction from pseudoaddiction can be difficult and often takes time and multiple patient encounters.

DEF-MDL-15455.00014


American Pain Society
Definitions Related to the
Use of Opioids for the Treatment of Pain

2001 ASAM

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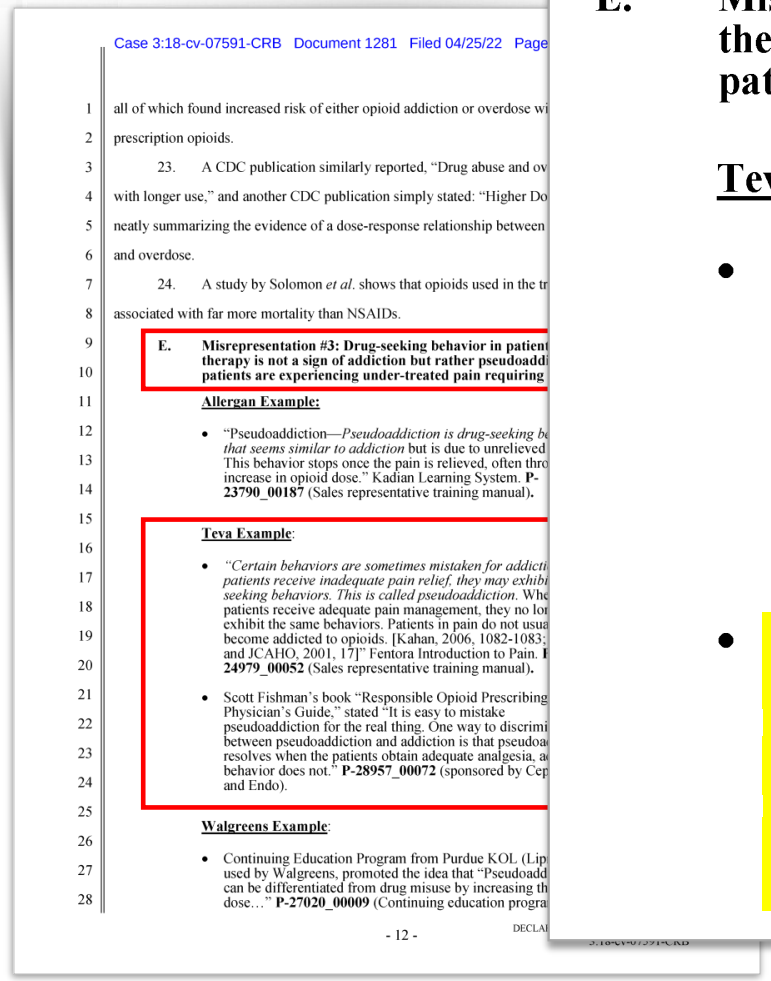
DEF-MDL-06142.00003

Declaration of Anna Lembke, M.D.



Case 3:18-cv-07591-CRB Document 1281 Filed 04/25/22 Page

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24. A study by Solomon *et al.* shows that opioids used in the tr
associated with far more mortality than NSAIDs.

E. Misrepresentation #3: Drug-seeking behavior in patient therapy is not a sign of addiction but rather pseudoaddi patients are experiencing under-treated pain requiring

Allergan Example:

- "Pseudoaddiction—*Pseudoaddiction is drug-seeking be that seems similar to addiction* but is due to unrelieved This behavior stops once the pain is relieved, often thro increase in opioid dose." Kadian Learning System. **P-23790_00187** (Sales representative training manual).

Teva Example:

- *"Certain behaviors are sometimes mistaken for addicti patients receive inadequate pain relief, they may exhibi seeking behaviors. This is called pseudoaddiction.* Whe patients receive adequate pain management, they no lo exhibit the same behaviors. Patients in pain do not usua become addicted to opioids. [Kahan, 2006, 1082-1083; and JCAHO, 2001, 17]" Fentora Introduction to Pain. **24979_00052** (Sales representative training manual).
- Scott Fishman's book "Responsible Opioid Prescribing Physician's Guide," stated "It is easy to mistake pseudoaddiction for the real thing. One way to discrimi between pseudoaddiction and addiction is that pseudoa resolves when the patients obtain adequate analgesia, a behavior does not." **P-28957_00072** (sponsored by Cep and Endo).

Walgreens Example:

- Continuing Education Program from Purdue KOL (Lip used by Walgreens, promoted the idea that "Pseudoadd can be differentiated from drug misuse by increasing th dose…" **P-27020_00009** (Continuing education progra

- 12 -

DECLAI

E. Misrepresentation #3: Drug-seeking behavior in patients receiving opioid therapy is not a sign of addiction but rather pseudoaddiction, and these patients are experiencing under-treated pain requiring more opioids.

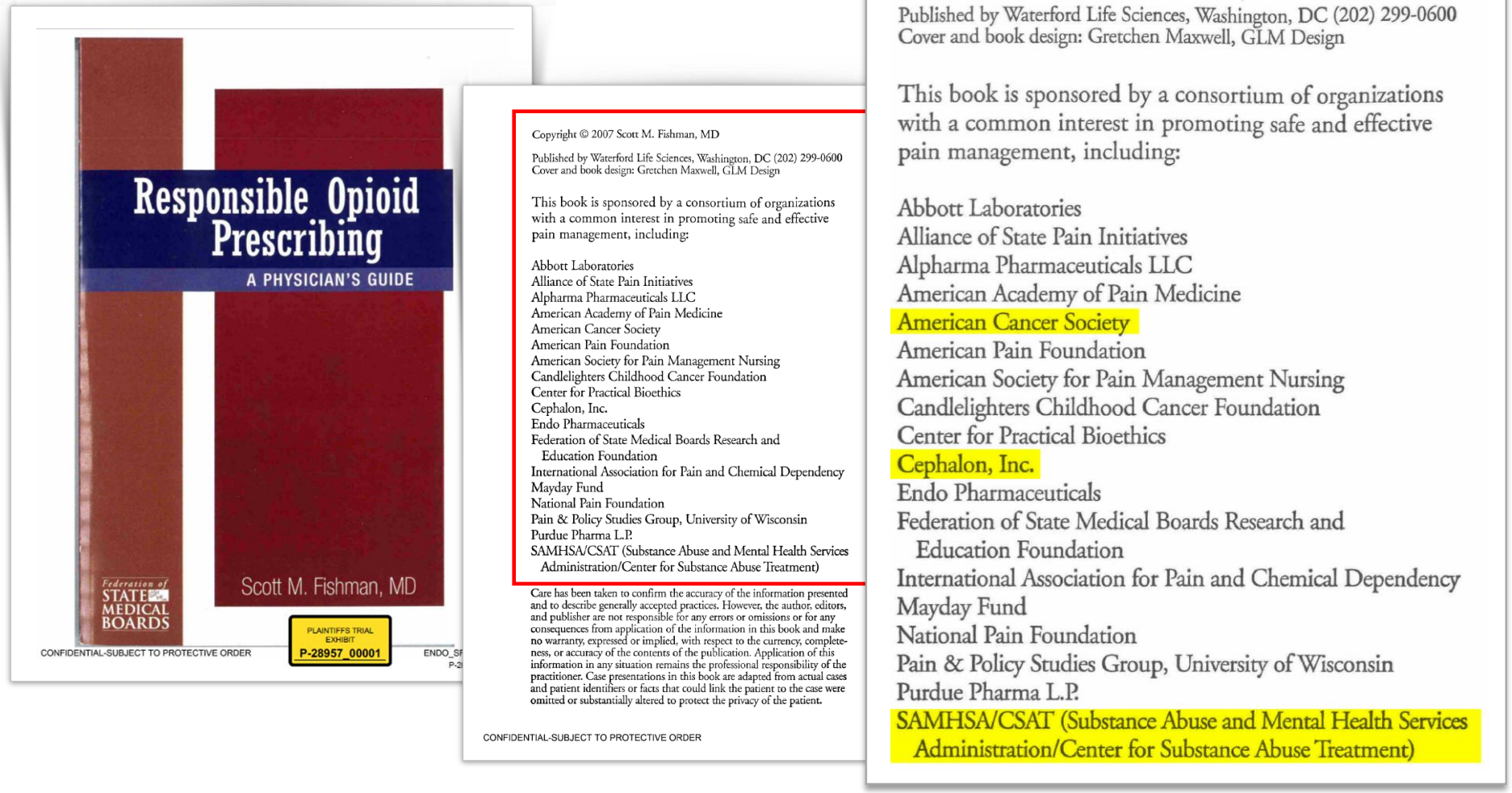
* * *

Teva Example:

- *"Certain behaviors are sometimes mistaken for addiction. If patients receive inadequate pain relief, they may exhibit drug-seeking behaviors. This is called pseudoaddiction*. When these patients receive adequate pain management, they no longer exhibit the same behaviors. Patients in pain do not usually become addicted to opioids. [Kahan, 2006, 1082-1083; NPC and JCAHO, 2001, 17]" Fentora Introduction to Pain. **P-24979_00052** (Sales representative training manual).
- Scott Fishman's book "Responsible Opioid Prescribing: A Physician's Guide," stated "It is easy to mistake pseudoaddiction for the real thing. One way to discriminate between pseudoaddiction and addiction is that pseudoaddiction resolves when the patients obtain adequate analgesia, addictive behavior does not." **P-28957_00072** (sponsored by Cephalon and Endo).

Lemke Decl. ¶ 24

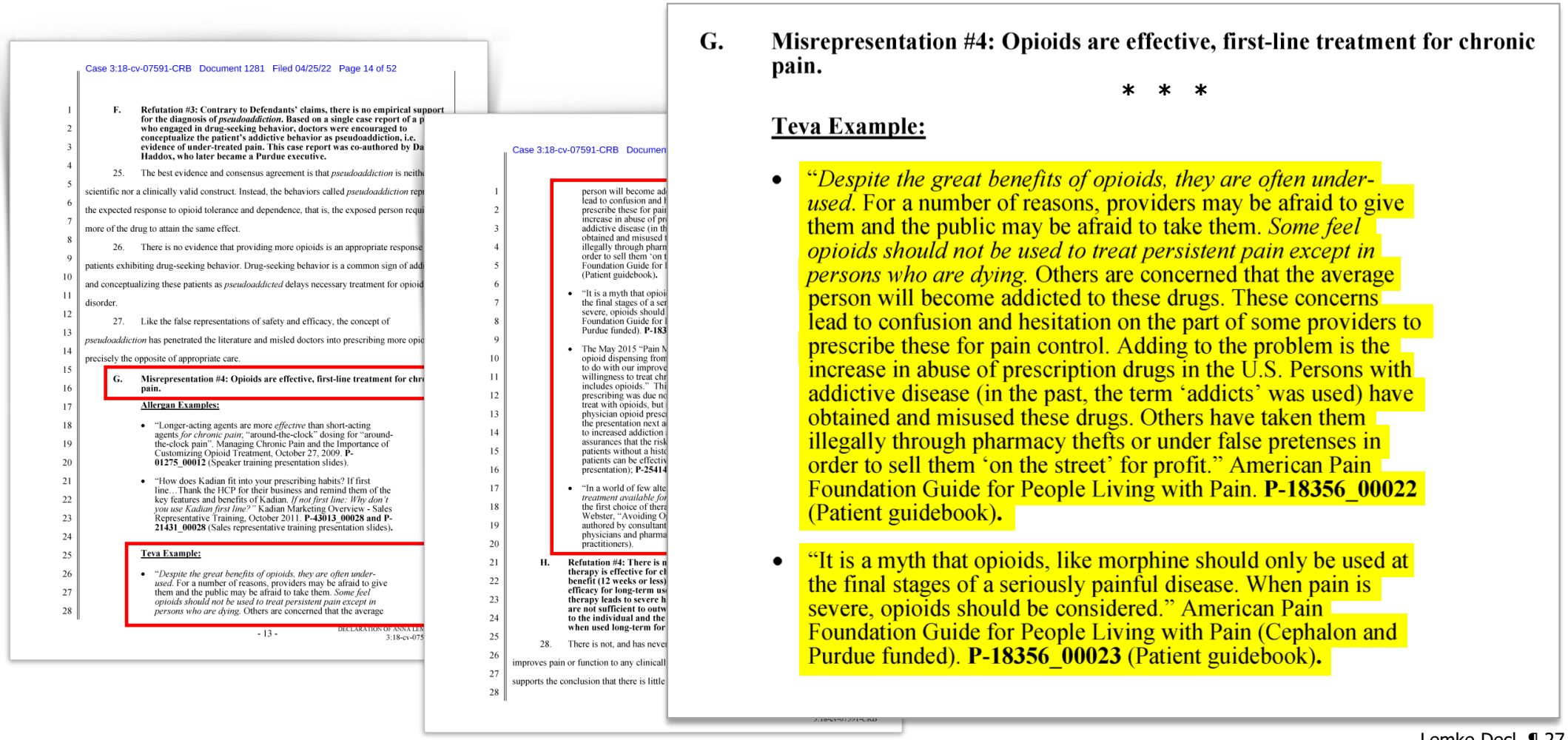
Scott Fishman's Responsible Opioid Prescribing (2007)



P-28957_00003

TCA Defendants Court Exhibit 00001.00041

Declaration of Anna Lembke, M.D.



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F. **Refutation #3: Contrary to Defendants' claims, there is no empirical support for the diagnosis of *pseudoaddiction*. Based on a single case report of a p who engaged in drug-seeking behavior, doctors were encouraged to conceptualize the patient's addictive behavior as pseudoaddiction, i.e. evidence of under-treated pain. This case report was co-authored by Da Haddox, who later became a Purdue executive.**

25. The best evidence and consensus agreement is that *pseudoaddiction* is neith scientific nor a clinically valid construct. Instead, the behaviors called *pseudoaddiction* repr the expected response to opioid tolerance and dependence, that is, the exposed person requi more of the drug to attain the same effect.

26. There is no evidence that providing more opioids is an appropriate response patients exhibiting drug-seeking behavior. Drug-seeking behavior is a common sign of addi and conceptualizing these patients as *pseudoaddicted* delays necessary treatment for opioid disorder.

27. Like the false representations of safety and efficacy, the concept of *pseudoaddiction* has penetrated the literature and misled doctors into prescribing more opio precisely the opposite of appropriate care.

G. **Misrepresentation #4: Opioids are effective, first-line treatment for chr pain.**

Allergan Examples:

- "Longer-acting agents are more *effective* than short-acting agents *for chronic pain*," "around-the-clock" dosing for "around-the-clock pain". Managing Chronic Pain and the Importance of Customizing Opioid Treatment, October 27, 2009. **P-01275_00012** (Speaker training presentation slides).
- "How does Kadian fit into your prescribing habits? If first line…Thank the HCP for their business and remind them of the key features and benefits of Kadian. *If not first line: Why don't you use Kadian first line?*" Kadian Marketing Overview - Sales Representative Training, October 2011. **P-43013_00028 and P-21431_00028** (Sales representative training presentation slides).

Teva Example:

- "*Despite the great benefits of opioids, they are often under-used*. For a number of reasons, providers may be afraid to give them and the public may be afraid to take them. *Some feel opioids should not be used to treat persistent pain except in persons who are dying*. Others are concerned that the average

- 13 -

DECLARATION OF ANNA LEM
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Foundation Guide for
(Patient guidebook).

- "It is a myth that opioi
the final stages of a ser
severe, opioids should
Foundation Guide for
Purdue funded). **P-183**

- The May 2015 "Pain M
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- "In a world of few alte
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Webster, "Avoiding O
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physicians and pharma
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H. **Refutation #4: There is n therapy is effective for ch benefit (12 weeks or less) efficacy for long-term us therapy leads to severe h are not sufficient to outw to the individual and the when used long-term for**

28. There is not, and has never improves pain or function to any clinicall supports the conclusion that there is little

G. Misrepresentation #4: Opioids are effective, first-line treatment for chronic pain.

* * *

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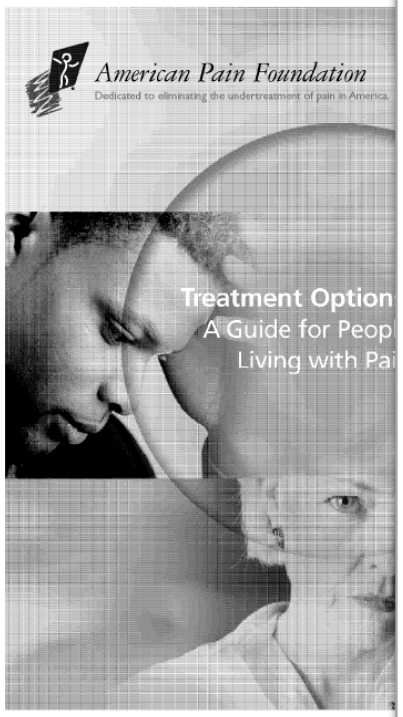
- "*Despite the great benefits of opioids, they are often under-used*. For a number of reasons, providers may be afraid to give them and the public may be afraid to take them. *Some feel opioids should not be used to treat persistent pain except in persons who are dying*. Others are concerned that the average person will become addicted to these drugs. These concerns lead to confusion and hesitation on the part of some providers to prescribe these for pain control. Adding to the problem is the increase in abuse of prescription drugs in the U.S. Persons with addictive disease (in the past, the term 'addicts' was used) have obtained and misused these drugs. Others have taken them illegally through pharmacy thefts or under false pretenses in order to sell them 'on the street' for profit." American Pain Foundation Guide for People Living with Pain. **P-18356_00022** (Patient guidebook).

- "It is a myth that opioids, like morphine should only be used at the final stages of a seriously painful disease. When pain is severe, opioids should be considered." American Pain Foundation Guide for People Living with Pain (Cephalon and Purdue funded). **P-18356_00023** (Patient guidebook).

Lemke Decl. ¶ 27

TCA Defendants Court Exhibit 00001.00042

Treatment Options: A Guide For People Living With Pain
American Pain Foundation (2007)



Confidential

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P-18356_00004

P-18356_00004

AVAILABLE TREATMENT OPTIONS

The following areas of pain treatment should be considered:

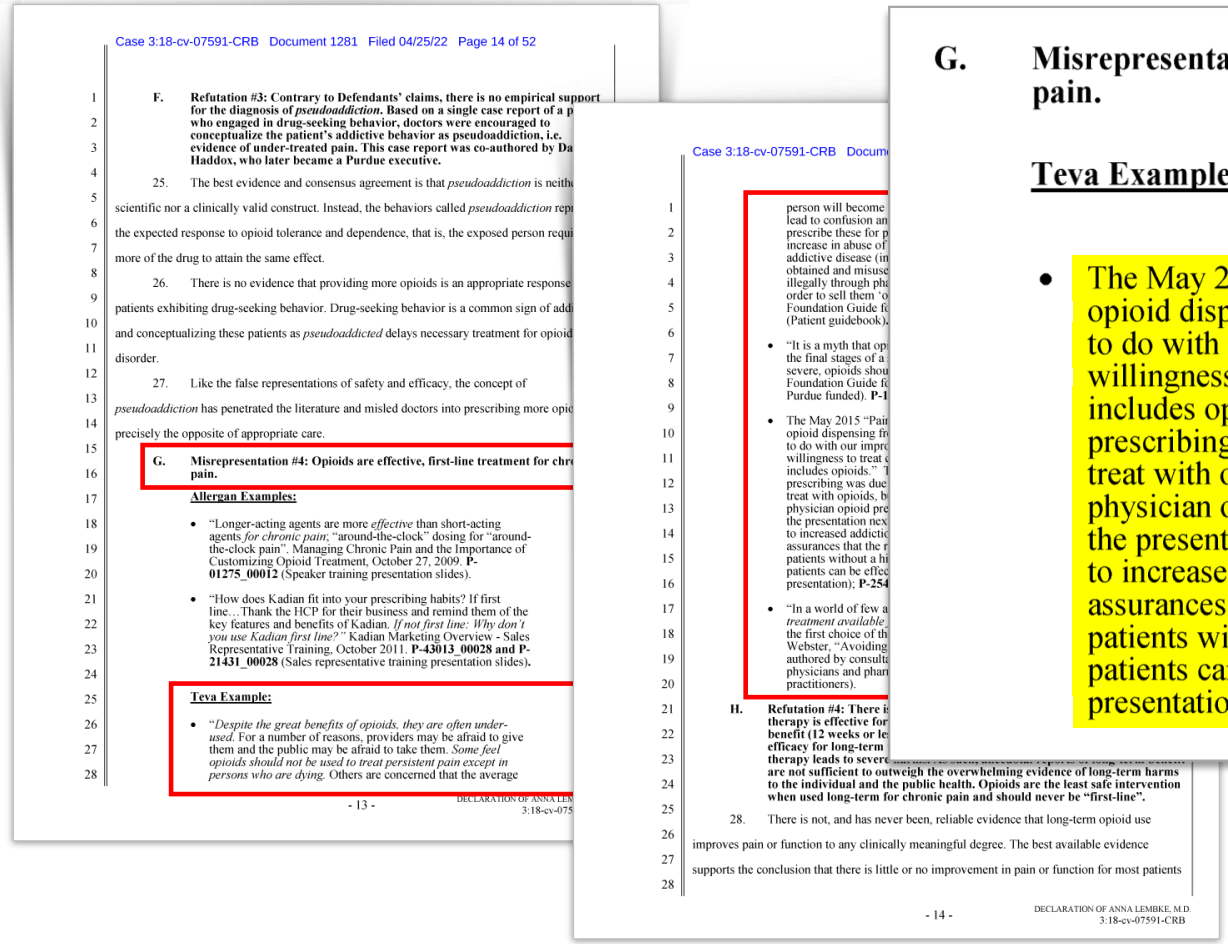
- Pharmacotherapy (drug options)
- Psychosocial Interventions (coping, counseling, etc.)
- Rehabilitation Techniques (re-conditioning, re-training and lifestyle changes)
- Complementary and Alternative Medicine (CAM)
- Injection and Infusion Therapies
- Implantable Devices and Surgical Interventions

Healthcare professionals who treat pain may not have experience in using or performing every treatment option available. Some pain treatment options require special areas of expertise or training. Referrals to those specialists may be required. Insurance coverage of pain treatment options vary widely, if covered at all.

The information in this guide is provided to help readers find answers and support. Readers are encouraged to share and discuss this information with their doctor.

P-18356_00017

Declaration of Anna Lembke, M.D.



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- 13 -

DECLARATION OF ANNA LEM
3:18-cv-075

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Purdue funded). **P-1**
- The May 2015 "Pain
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assurances that the r
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patients can be effec
presentation); **P-254**
- "In a world of few a
treatment available
the first choice of th
Webster, "Avoiding
authored by consulti
physicians and phar
practitioners).

H. **Refutation #4: There i therapy is effective for benefit (12 weeks or le efficacy for long-term therapy leads to severe are not sufficient to outweigh the overwhelming evidence of long-term harms to the individual and the public health. Opioids are the least safe intervention when used long-term for chronic pain and should never be "first-line".**

28. There is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically meaningful degree. The best available evidence supports the conclusion that there is little or no improvement in pain or function for most patients

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DECLARATION OF ANNA LEMBKE, M.D.
3:18-cv-07591-CRB

G. Misrepresentation #4: Opioids are effective, first-line treatment for chronic pain.

* * *

Teva Example:

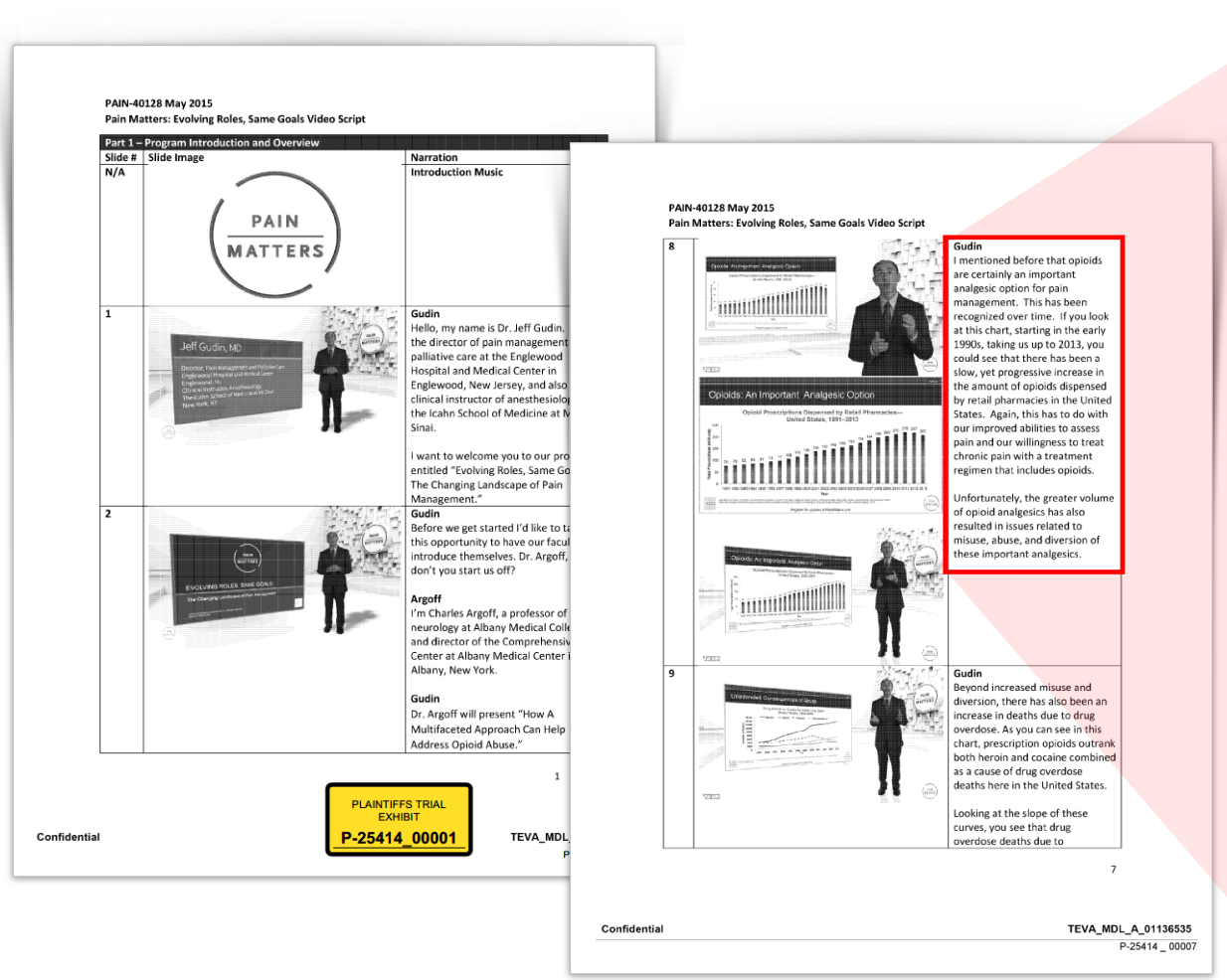
* * *

- The May 2015 "Pain Matters" presentation showing increased opioid dispensing from 1990s to 2013 explained that "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." This is misleading because the increased in prescribing was due not to improved abilities to assess pain and treat with opioids, but rather due to the paradigm shift in physician opioid prescribing caused by overpromotion. While the presentation next acknowledges increased prescribing leads to increased addiction and abuse, it follows with misleading assurances that the risks are relatively low, especially for patients without a history of abuse and addiction, and that patients can be effectively screened. **P-18318** (speaker video presentation); **P-25414_00007** (script).

Lemke Decl. ¶ 27

TCA Defendants Court Exhibit 00001.00044

Pain Matters Script (2015)



PAIN-40128 May 2015
Pain Matters: Evolving Roles, Same Goals Video Script

Part 1 – Program Introduction and Overview

Slide #	Slide Image	Narration
N/A	PAIN MATTERS	Introduction Music
1	Jeff Gudin, MD	**Gudin** Hello, my name is Dr. Jeff Gudin, the director of pain management palliative care at the Englewood Hospital and Medical Center in Englewood, New Jersey, and also clinical instructor of anesthesiolo the Icahn School of Medicine at M Sinai. I want to welcome you to our pro entitled "Evolving Roles, Same Go The Changing Landscape of Pain Management."
2	EVOLVING ROLES, SAME GOALS	**Gudin** Before we get started I'd like to ta this opportunity to have our facul introduce themselves. Dr. Argoff, don't you start us off? **Argoff** I'm Charles Argoff, a professor of neurology at Albany Medical Coll and director of the Comprehensiv Center at Albany Medical Center i Albany, New York. **Gudin** Dr. Argoff will present "How A Multifaceted Approach Can Help Address Opioid Abuse."

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PLAINTIFFS TRIAL EXHIBIT
P-25414_00001

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PAIN-40128 May 2015
Pain Matters: Evolving Roles, Same Goals Video Script

8	Opioids: An Important Analgesic Option	**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	**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

7

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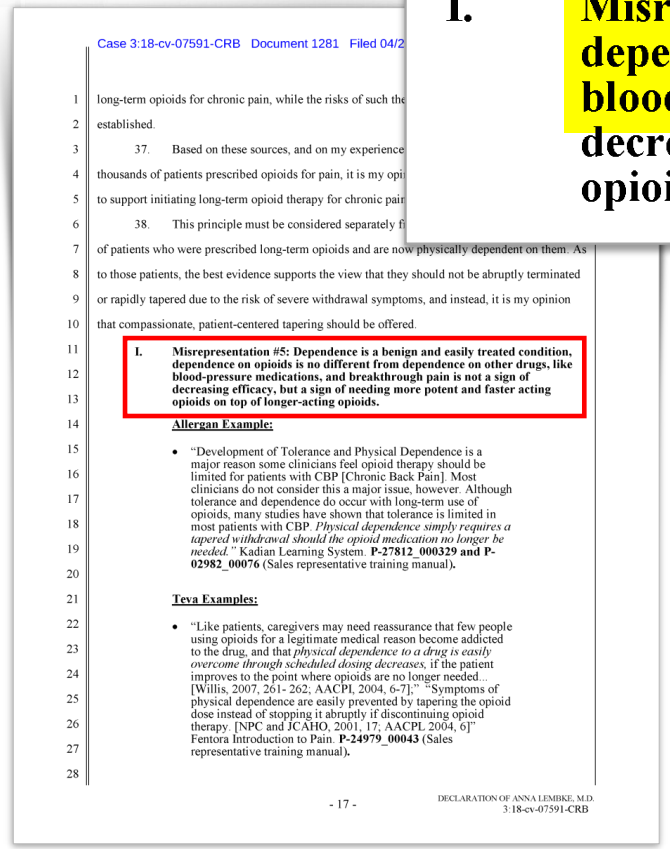
P-25414_00007

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.

TCA Defendants Court Exhibit 00001.00045

Declaration of Anna Lembke, M.D.



Case 3:18-cv-07591-CRB Document 1281 Filed 04/2

long-term opioids for chronic pain, while the risks of such the established.

37. Based on these sources, and on my experience thousands of patients prescribed opioids for pain, it is my opi to support initiating long-term opioid therapy for chronic pain

38. This principle must be considered separately fi of patients who were prescribed long-term opioids and are now physically dependent on them. As to those patients, the best evidence supports the view that they should not be abruptly terminated or rapidly tapered due to the risk of severe withdrawal symptoms, and instead, it is my opinion that compassionate, patient-centered tapering should be offered.

I. Misrepresentation #5: Dependence is a benign and easily treated condition, dependence on opioids is no different from dependence on other drugs, like blood-pressure medications, and breakthrough pain is not a sign of decreasing efficacy, but a sign of needing more potent and faster acting opioids on top of longer-acting opioids.

Allergan Example:

- "Development of Tolerance and Physical Dependence is a major reason some clinicians feel opioid therapy should be limited for patients with CBP [Chronic Back Pain]. Most clinicians do not consider this a major issue, however. Although tolerance and dependence do occur with long-term use of opioids, many studies have shown that tolerance is limited in most patients with CBP. *Physical dependence simply requires a tapered withdrawal should the opioid medication no longer be needed.*" Kadian Learning System. **P-27812_000329 and P-02982_00076** (Sales representative training manual).

Teva Examples:

- "Like patients, caregivers may need reassurance that few people using opioids for a legitimate medical reason become addicted to the drug, and that *physical dependence to a drug is easily overcome through scheduled dosing decreases*, if the patient improves to the point where opioids are no longer needed… [Willis, 2007, 261- 262; AACPI, 2004, 6-7];" "Symptoms of physical dependence are easily prevented by tapering the opioid dose instead of stopping it abruptly if discontinuing opioid therapy. [NPC and JCAHO, 2001, 17; AACPL 2004, 6]" Fentora Introduction to Pain. **P-24979_00043** (Sales representative training manual).

- 17 -

DECLARATION OF ANNA LEMBKE, M.D.
3:18-cv-07591-CRB

I. Misrepresentation #5: Dependence is a benign and easily treated condition, dependence on opioids is no different from dependence on other drugs, like blood-pressure medications, and breakthrough pain is not a sign of decreasing efficacy, but a sign of needing more potent and faster acting opioids on top of longer-acting opioids.

Lemke Decl. ¶ 38

TCA Defendants Court Exhibit 00001.00046

Declaration of Anna Lembke, M.D.

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Lemke Decl. ¶ 38

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long-term opioids for chronic pain, while the risks of such therapy are significant and well-established.

37. Based on these sources, and on my experience as a physician having treated thousands of patients prescribed opioids for pain, it is my opinion that the evidence is insufficie to support initiating long-term opioid therapy for chronic pain in the vast majority of cases.

38. This principle must be considered separately from the proper care of the million of patients who were prescribed long-term opioids and are now physically dependent on them. to those patients, the best evidence supports the view that they should not be abruptly terminate or rapidly tapered due to the risk of severe withdrawal symptoms, and instead, it is my opinion that compassionate, patient-centered tapering should be offered.

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Teva Examples:

- "Like patients, caregivers may need reassurance that few people using opioids for a legitimate medical reason become addicted to the drug, and that *physical dependence to a drug is easily overcome through scheduled dosing decreases,* if the patient improves to the point where opioids are no longer needed... [Willis, 2007, 261- 262; AACPI, 2004, 6-7];" "Symptoms of physical dependence are easily prevented by tapering the opioid dose instead of stopping it abruptly if discontinuing opioid therapy. [NPC and JCAHO, 2001, 17; AACPL 2004, 6]" Fentora Introduction to Pain. **P-24979_00043** (Sales representative training manual).

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DECLARATION OF ANNA LEMBKE
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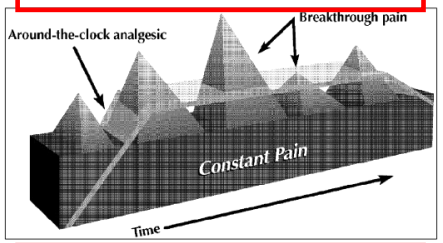
Case 3:18-cv-07591-CRB

- *"Physical dependence is normal*; any patient who is taking an opioid on a regular basis for a few days should be assumed to be physically dependent. This does NOT mean you are addicted. In fact, many non-addictive drugs can produce physical dependence. To prevent withdrawal from occurring, *the dose of the medication must be decreased slowly."* American Pain Foundation Guide for People Living with Pain. **P-18356_00025** (Patient guidebook).

- "Fentanyl is also available in a lozenge. In this formulation, it has a quick onset and short duration of effect that makes it *especially useful for the treatment of 'breakthrough' pain."* American Pain Foundation Guide for People Living with Pain. **P-18356_00024** (Patient guidebook). This statement and the image below imply that adding fast-acting, lethal opioids like fentanyl can address this problem. For someone at the very end of life this may be appropriate, but for someone with chronic pain, this type of intervention increases dose and with it risk of morbidity and mortality. Figure 6 illustrates the image that Teva used to describe breakthrough pain [Payne, 2007, S3; Portenoy, 2006, 586; Davis, 2004, 629.]" Fentora Introduction to Pain. **P-24979_00031** (Sales representative training manual). Figure 6 is reproduced below:



- *"Breakthrough pain is often managed by adding a medication* in addition to the drug used for the persistent pain. [Payne, 2007, S4-S5; Duragesic, 2008, 1]" Fentora Introduction to Pain. **P-24979_00038** (Sales representative training manual).

- "Third, frequent pain reassessment will help gauge the effectiveness of analgesic therapy. Assessment may help health care professionals choose more effective agents, titrate the dose or dosing interval appropriately, check the usefulness of the current route of administration, manage side effects, and *assess the need for more effective breakthrough pain medication alongside the around-the-clock medication.* [Carver. 2005, 10-

- 18 -

3:18-cv-07591-C

Case 3:18-cv-07591-CRB Document 1281 Filed 04/25/22 Page 20 of 52

11; McCarberg, 2007, S8]" Fentora Introduction to Pain. **P-24979_00038** (Sales representative training manual).

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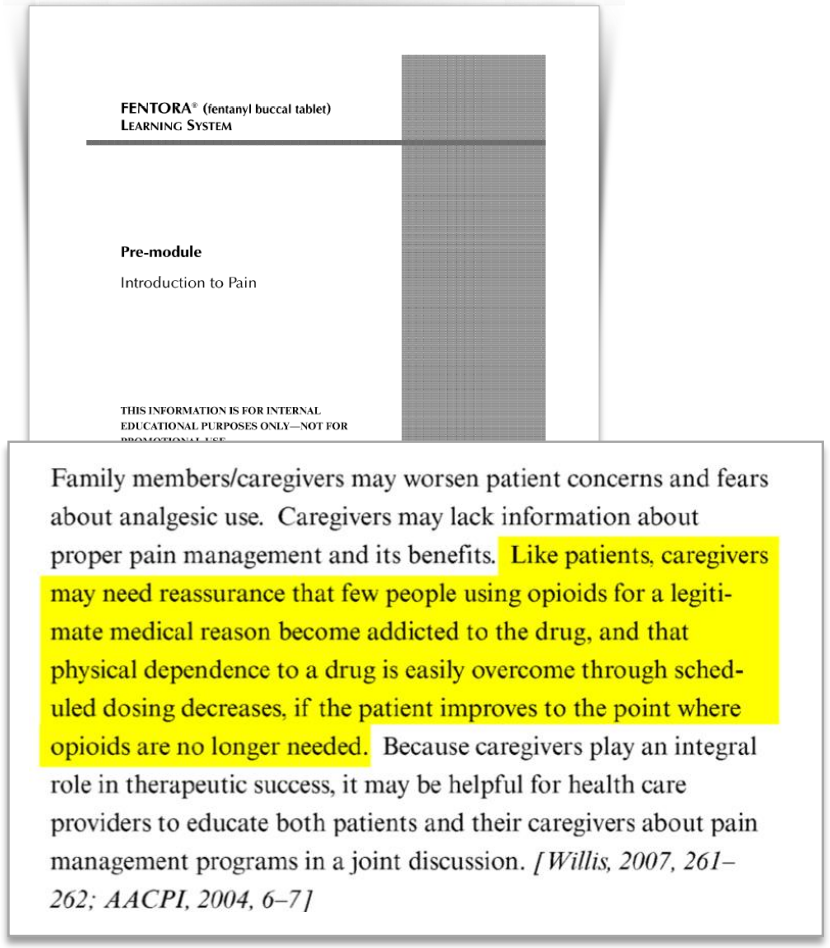
Lemke Decl. ¶ 38

TCA Defendants Court Exhibit 00001.00047

Fentora Introduction to Pain (2008) & Treatment Options: A Guide For People Living With Pain (2007)



FENTORA® (fentanyl buccal tablet)
LEARNING SYSTEM

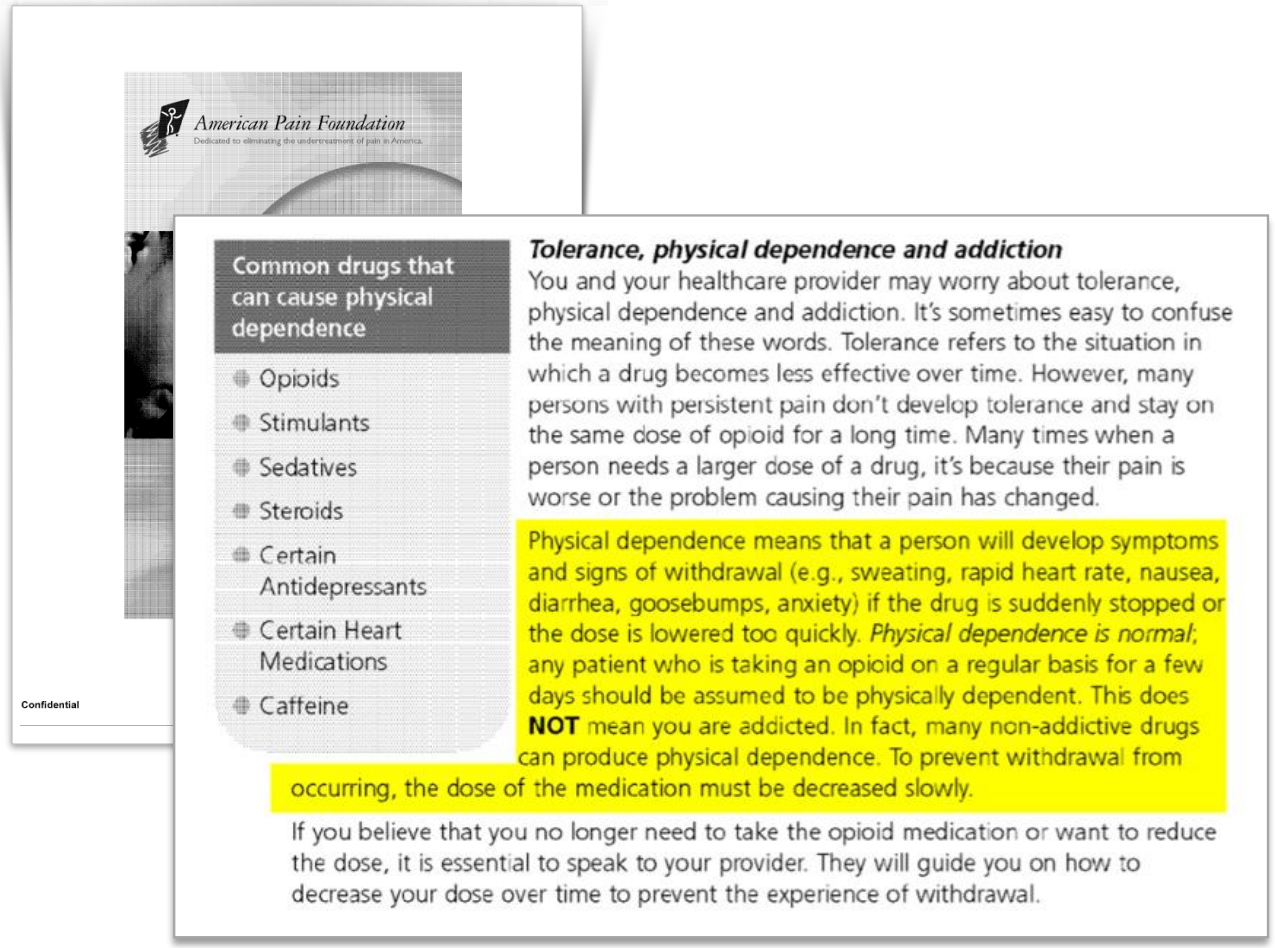
Pre-module

Introduction to Pain

THIS INFORMATION IS FOR INTERNAL EDUCATIONAL PURPOSES ONLY—NOT FOR PROMOTIONAL USE

Family members/caregivers may worsen patient concerns and fears about analgesic use. Caregivers may lack information about proper pain management and its benefits. Like patients, caregivers may need reassurance that few people using opioids for a legitimate medical reason become addicted to the drug, and that physical dependence to a drug is easily overcome through scheduled dosing decreases, if the patient improves to the point where opioids are no longer needed. Because caregivers play an integral role in therapeutic success, it may be helpful for health care providers to educate both patients and their caregivers about pain management programs in a joint discussion. *[Willis, 2007, 261–262; AACPI, 2004, 6–7]*

P-24979_00043



American Pain Foundation
Dedicated to eliminating the undertreatment of pain in America

Confidential

Common drugs that can cause physical dependence

- Opioids
- Stimulants
- Sedatives
- Steroids
- Certain Antidepressants
- Certain Heart Medications
- Caffeine

Tolerance, physical dependence and addiction

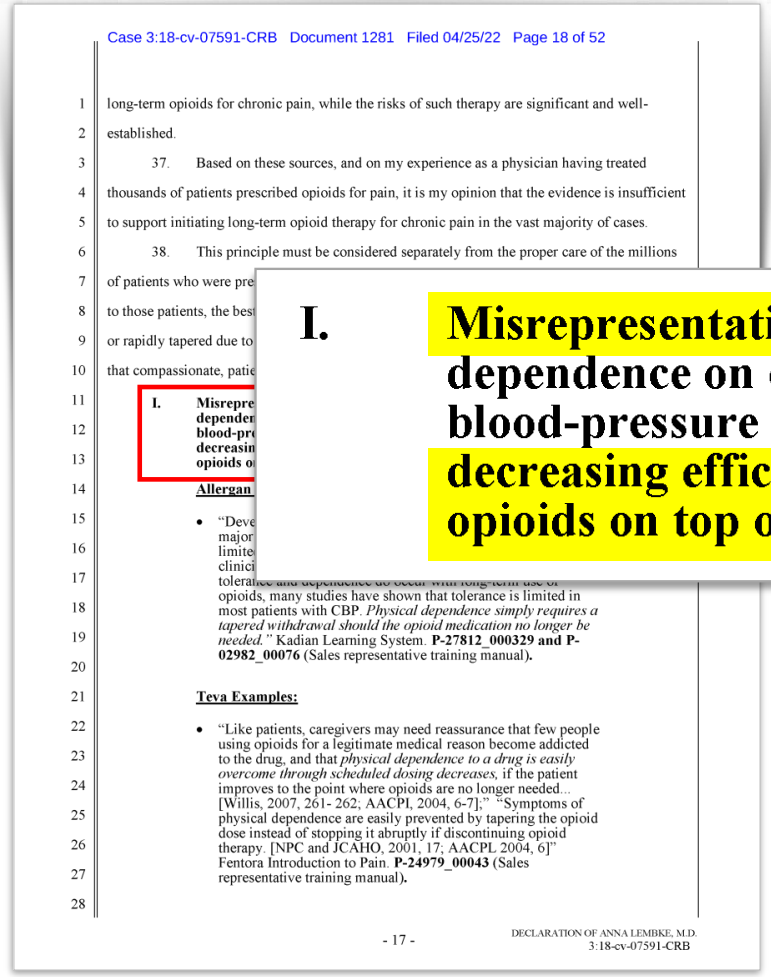
You and your healthcare provider may worry about tolerance, physical dependence and addiction. It's sometimes easy to confuse the meaning of these words. Tolerance refers to the situation in which a drug becomes less effective over time. However, many persons with persistent pain don't develop tolerance and stay on the same dose of opioid for a long time. Many times when a person needs a larger dose of a drug, it's because their pain is worse or the problem causing their pain has changed.

Physical dependence means that a person will develop symptoms and signs of withdrawal (e.g., sweating, rapid heart rate, nausea, diarrhea, goosebumps, anxiety) if the drug is suddenly stopped or the dose is lowered too quickly. *Physical dependence is normal*; any patient who is taking an opioid on a regular basis for a few days should be assumed to be physically dependent. This does **NOT** mean you are addicted. In fact, many non-addictive drugs can produce physical dependence. To prevent withdrawal from occurring, the dose of the medication must be decreased slowly.

If you believe that you no longer need to take the opioid medication or want to reduce the dose, it is essential to speak to your provider. They will guide you on how to decrease your dose over time to prevent the experience of withdrawal.

P-18356_00025

Declaration of Anna Lembke, M.D.



Case 3:18-cv-07591-CRB Document 1281 Filed 04/25/22 Page 18 of 52

long-term opioids for chronic pain, while the risks of such therapy are significant and well-established.

37. Based on these sources, and on my experience as a physician having treated thousands of patients prescribed opioids for pain, it is my opinion that the evidence is insufficient to support initiating long-term opioid therapy for chronic pain in the vast majority of cases.

38. This principle must be considered separately from the proper care of the millions of patients who were pre
to those patients, the best
or rapidly tapered due to
that compassionate, patie

I. Misrepre
depender
blood-pre
decreasin
opioids o

Allergan

- "Deve
major
limite
clinici
tolera
opioids, many studies have shown that tolerance is limited in most patients with CBP. *Physical dependence simply requires a tapered withdrawal should the opioid medication no longer be needed."* Kadian Learning System. **P-27812_000329 and P-02982_00076** (Sales representative training manual).

Teva Examples:

- "Like patients, caregivers may need reassurance that few people using opioids for a legitimate medical reason become addicted to the drug, and that *physical dependence to a drug is easily overcome through scheduled dosing decreases,* if the patient improves to the point where opioids are no longer needed... [Willis, 2007, 261- 262; AACPI, 2004, 6-7];" "Symptoms of physical dependence are easily prevented by tapering the opioid dose instead of stopping it abruptly if discontinuing opioid therapy. [NPC and JCAHO, 2001, 17; AACPL 2004, 6]" Fentora Introduction to Pain. **P-24979_00043** (Sales representative training manual).

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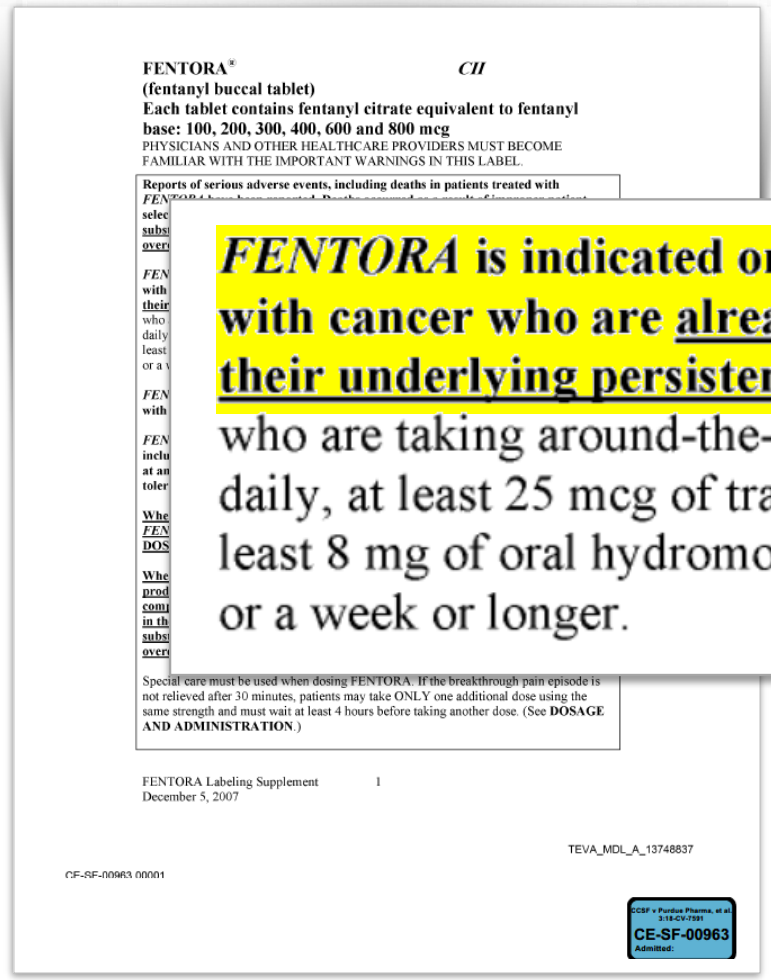
DECLARATION OF ANNA LEMBKE, M.D.
3:18-cv-07591-CRB

I. Misrepresentation #5: Dependence is a benign and easily treated condition, dependence on opioids is no different from dependence on other drugs, like blood-pressure medications, and breakthrough pain is not a sign of decreasing efficacy, but a sign of needing more potent and faster acting opioids on top of longer-acting opioids.

Lemke Decl. ¶ 38

TCA Defendants Court Exhibit 00001.00049

Fentora FDA Approved Label (2007)



FENTORA® *CII*
(fentanyl buccal tablet)
Each tablet contains fentanyl citrate equivalent to fentanyl base: 100, 200, 300, 400, 600 and 800 mcg
PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

Reports of serious adverse events, including deaths in patients treated with

Special care must be used when dosing FENTORA. If the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY one additional dose using the same strength and must wait at least 4 hours before taking another dose. (See **DOSAGE AND ADMINISTRATION**.)

FENTORA Labeling Supplement 1
December 5, 2007

TEVA_MDL_A_13748837

CE-SF-00963 00001

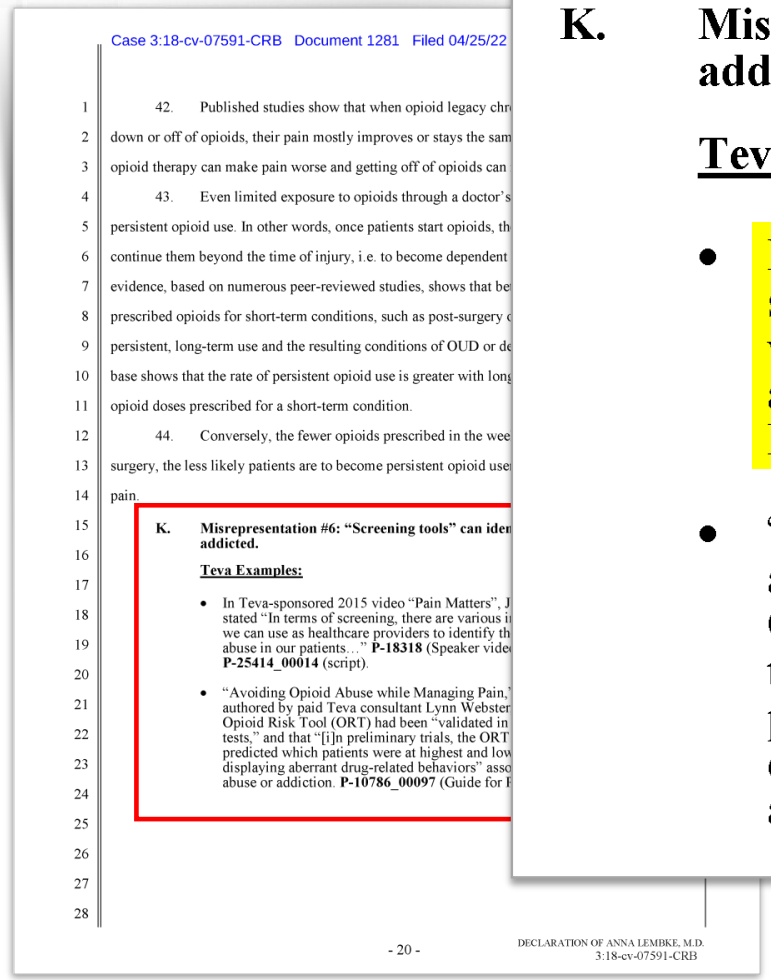
CCSF v Purdue Pharma, et al.
3:18-CV-7591
CE-SF-00963
Admitted:

***FENTORA* is indicated only for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily or a week or longer.

CE-SF-00963.0001

TCA Defendants Court Exhibit 00001.00050

Declaration of Anna Lembke, M.D.


Case 3:18-cv-07591-CRB Document 1281 Filed 04/25/22

42. Published studies show that when opioid legacy chr
down or off of opioids, their pain mostly improves or stays the sam
opioid therapy can make pain worse and getting off of opioids can

43. Even limited exposure to opioids through a doctor's
persistent opioid use. In other words, once patients start opioids, th
continue them beyond the time of injury, i.e. to become dependent
evidence, based on numerous peer-reviewed studies, shows that be
prescribed opioids for short-term conditions, such as post-surgery
persistent, long-term use and the resulting conditions of OUD or de
base shows that the rate of persistent opioid use is greater with long
opioid doses prescribed for a short-term condition.

44. Conversely, the fewer opioids prescribed in the wee
surgery, the less likely patients are to become persistent opioid use
pain.

K. Misrepresentation #6: "Screening tools" can iden addicted.

Teva Examples:

- In Teva-sponsored 2015 video "Pain Matters", J stated "In terms of screening, there are various i we can use as healthcare providers to identify th abuse in our patients…" **P-18318** (Speaker vide **P-25414_00014** (script).
- "Avoiding Opioid Abuse while Managing Pain," authored by paid Teva consultant Lynn Webster Opioid Risk Tool (ORT) had been "validated in tests," and that "[i]n preliminary trials, the ORT predicted which patients were at highest and low displaying aberrant drug-related behaviors" asso abuse or addiction. **P-10786_00097** (Guide for P

- 20 -

DECLARATION OF ANNA LEMBKE, M.D.
3:18-cv-07591-CRB

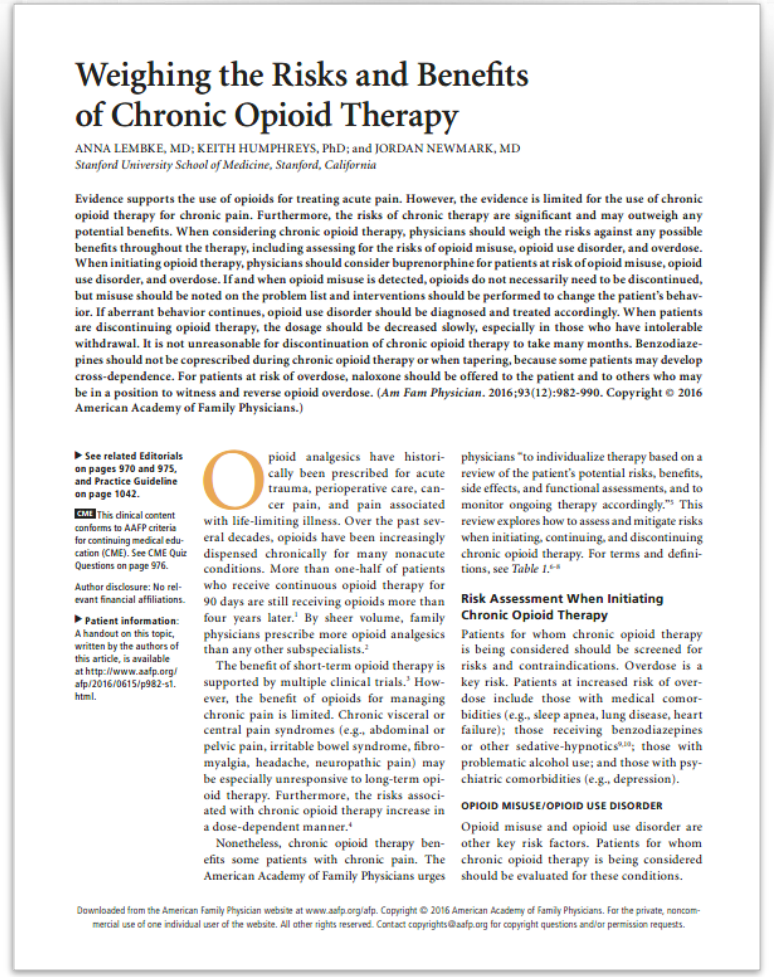
K. Misrepresentation #6: "Screening tools" can identify who will become addicted.

Teva Examples:

- In Teva-sponsored 2015 video "Pain Matters", Jeffrey Gudin stated "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…" **P-18318** (Speaker video presentation); **P-25414_00014** (script).
- "Avoiding Opioid Abuse while Managing Pain," a book authored by paid Teva consultant Lynn Webster, stated that the Opioid Risk Tool (ORT) had been "validated in initial clinical tests," and that "[i]n preliminary trials, the ORT accurately predicted which patients were at highest and lowest risk for displaying aberrant drug-related behaviors" associated with abuse or addiction. **P-10786_00097** (Guide for Practitioners).

Lemke Decl. ¶ 44

Anna Lembke: Weighing the Risks and Benefits of Chronic Opioid Therapy (2016)



Weighing the Risks and Benefits of Chronic Opioid Therapy

ANNA LEMBKE, MD; KEITH HUMPHREYS, PhD; and JORDAN NEWMARK, MD
Stanford University School of Medicine, Stanford, California

Evidence supports the use of opioids for treating acute pain. However, the evidence is limited for the use of chronic opioid therapy for chronic pain. Furthermore, the risks of chronic therapy are significant and may outweigh any potential benefits. When considering chronic opioid therapy, physicians should weigh the risks against any possible benefits throughout the therapy, including assessing for the risks of opioid misuse, opioid use disorder, and overdose. When initiating opioid therapy, physicians should consider buprenorphine for patients at risk of opioid misuse, opioid use disorder, and overdose. If and when opioid misuse is detected, opioids do not necessarily need to be discontinued, but misuse should be noted on the problem list and interventions should be performed to change the patient's behavior. If aberrant behavior continues, opioid use disorder should be diagnosed and treated accordingly. When patients are discontinuing opioid therapy, the dosage should be decreased slowly, especially in those who have intolerable withdrawal. It is not unreasonable for discontinuation of chronic opioid therapy to take many months. Benzodiazepines should not be coprescribed during chronic opioid therapy or when tapering, because some patients may develop cross-dependence. For patients at risk of overdose, naloxone should be offered to the patient and to others who may be in a position to witness and reverse opioid overdose. (*Am Fam Physician*. 2016;93(12):982-990. Copyright © 2016 American Academy of Family Physicians.)

▶ **See related Editorials on pages 970 and 975, and Practice Guideline on page 1042.**

CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz Questions on page 976.

Author disclosure: No relevant financial affiliations.

▶ **Patient information:** A handout on this topic, written by the authors of this article, is available at http://www.aafp.org/afp/2016/0615/p982-s1.html.

Opioid analgesics have historically been prescribed for acute trauma, perioperative care, cancer pain, and pain associated with life-limiting illness. Over the past several decades, opioids have been increasingly dispensed chronically for many nonacute conditions. More than one-half of patients who receive continuous opioid therapy for 90 days are still receiving opioids more than four years later.[1] By sheer volume, family physicians prescribe more opioid analgesics than any other subspecialists.[2]

The benefit of short-term opioid therapy is supported by multiple clinical trials.[3] However, the benefit of opioids for managing chronic pain is limited. Chronic visceral or central pain syndromes (e.g., abdominal or pelvic pain, irritable bowel syndrome, fibromyalgia, headache, neuropathic pain) may be especially unresponsive to long-term opioid therapy. Furthermore, the risks associated with chronic opioid therapy increase in a dose-dependent manner.[4]

Nonetheless, chronic opioid therapy benefits some patients with chronic pain. The American Academy of Family Physicians urges physicians "to individualize therapy based on a review of the patient's potential risks, benefits, side effects, and functional assessments, and to monitor ongoing therapy accordingly."[5] This review explores how to assess and mitigate risks when initiating, continuing, and discontinuing chronic opioid therapy. For terms and definitions, see *Table 1*.[6-8]

Risk Assessment When Initiating Chronic Opioid Therapy

Patients for whom chronic opioid therapy is being considered should be screened for risks and contraindications. Overdose is a key risk. Patients at increased risk of overdose include those with medical comorbidities (e.g., sleep apnea, lung disease, heart failure); those receiving benzodiazepines or other sedative-hypnotics[9,10]; those with problematic alcohol use; and those with psychiatric comorbidities (e.g., depression).

OPIOID MISUSE/OPIOID USE DISORDER

Opioid misuse and opioid use disorder are other key risk factors. Patients for whom chronic opioid therapy is being considered should be evaluated for these conditions.

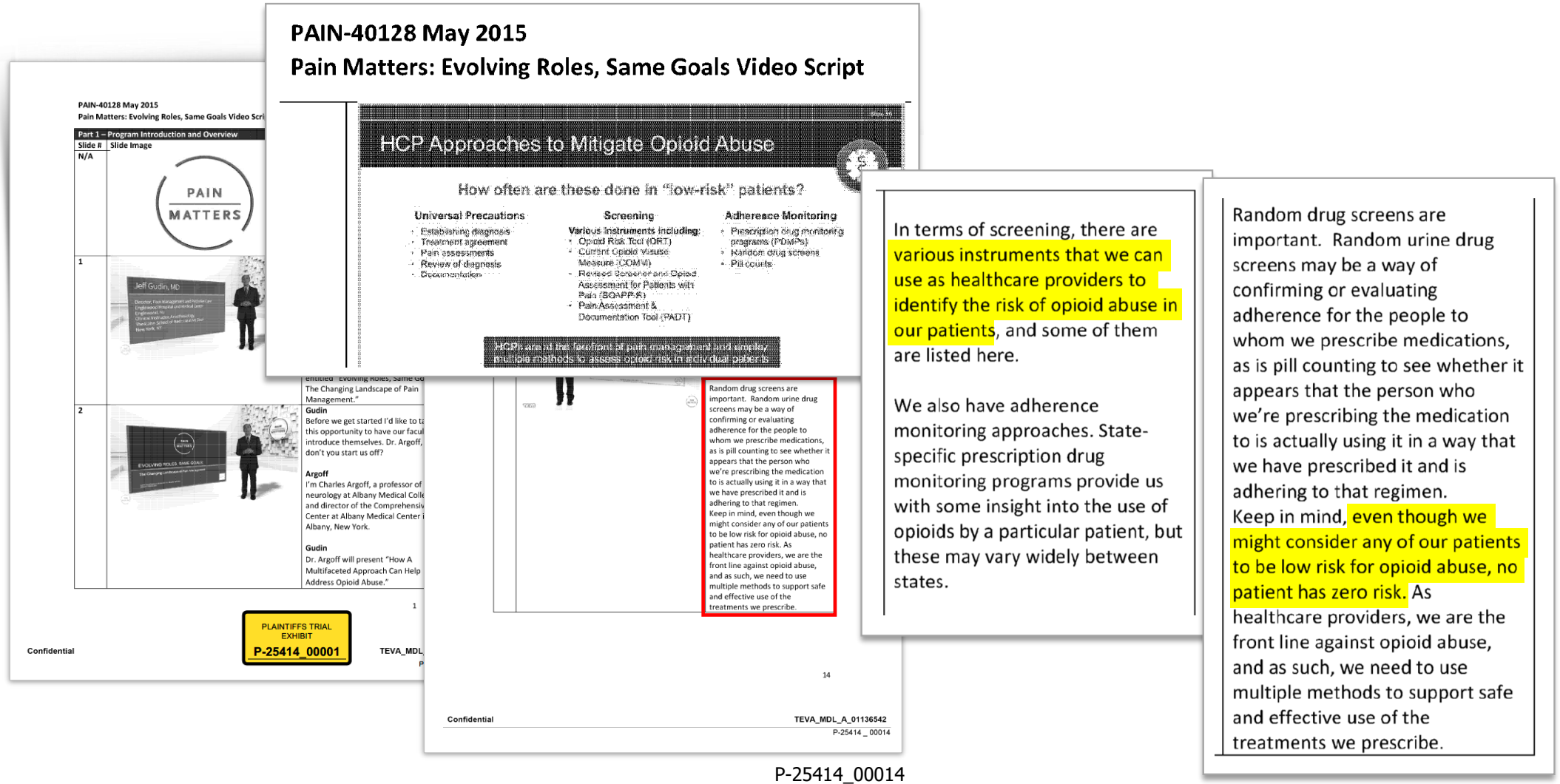
Risk Assessment When Initiating Chronic Opioid Therapy

Patients for whom chronic opioid therapy is being considered should be screened for risks and contraindications. Overdose is a key risk. Patients at increased risk of overdose include those with medical comorbidities (e.g., sleep apnea, lung disease, heart failure); those receiving benzodiazepines or other sedative-hypnotics[9,10]; those with problematic alcohol use; and those with psychiatric comorbidities (e.g., depression).

DEF-MDL-10700.00001

TCA Defendants Court Exhibit 00001.00052

Pain Matters Script (2015)



PAIN-40128 May 2015

Pain Matters: Evolving Roles, Same Goals Video Script

Part 1 – Program Introduction and Overview

Slide #	Slide Image
N/A	PAIN MATTERS
1	Jeff Gudin, MD
2	EVOLVING ROLES, SAME GOALS

The Changing Landscape of Pain Management."

Gudin
Before we get started I'd like to ta
this opportunity to have our facul
introduce themselves. Dr. Argoff,
don't you start us off?

Argoff
I'm Charles Argoff, a professor of
neurology at Albany Medical Coll
and director of the Comprehensiv
Center at Albany Medical Center i
Albany, New York.

Gudin
Dr. Argoff will present "How A Multifaceted Approach Can Help Address Opioid Abuse."

1

PLAINTIFFS TRIAL EXHIBIT
P-25414_00001

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TEVA_MDL

PAIN-40128 May 2015

Pain Matters: Evolving Roles, Same Goals Video Script

HCP Approaches to Mitigate Opioid Abuse

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

Universal Precautions	Screening	Adherence Monitoring
• Establishing diagnosis • Treatment agreement • Pain assessments • Review of diagnosis • Documentation	Various instruments including: • Opioid Risk Tool (ORT) • Current Opioid Misuse Measure (COMM) • Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R) • Pain Assessment & Documentation Tool (PADT)	• Prescription drug monitoring programs (PDMPs) • Random drug screens • Pill counts

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

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.

14

Confidential

TEVA_MDL_A_01136542

P-25414 _ 00014

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.

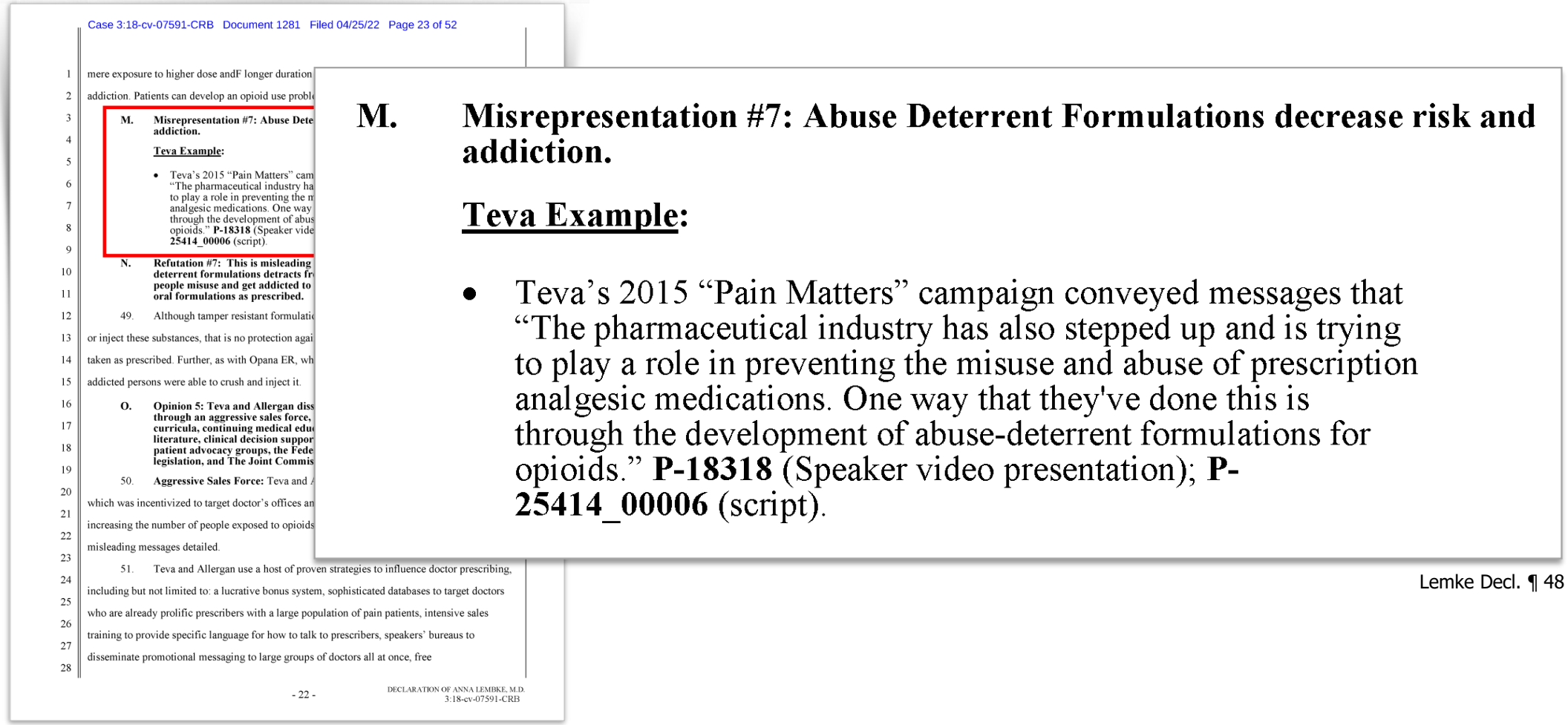
We also have adherence monitoring approaches. State-specific prescription drug monitoring programs provide us with some insight into the use of opioids by a particular patient, but these may vary widely between states.

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.

P-25414_00014

TCA Defendants Court Exhibit 00001.00053

Declaration of Anna Lembke, M.D.



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mere exposure to higher dose andF longer duration

addiction. Patients can develop an opioid use proble

M. Misrepresentation #7: Abuse Dete addiction.

Teva Example:

- Teva's 2015 "Pain Matters" cam "The pharmaceutical industry ha to play a role in preventing the n analgesic medications. One way through the development of abus opioids." **P-18318** (Speaker vide **25414_00006** (script).

N. Refutation #7: This is misleading deterrent formulations detracts fr people misuse and get addicted to oral formulations as prescribed.

49. Although tamper resistant formulati

or inject these substances, that is no protection agai

taken as prescribed. Further, as with Opana ER, wh

addicted persons were able to crush and inject it.

O. Opinion 5: Teva and Allergan diss through an aggressive sales force, curricula, continuing medical edu literature, clinical decision suppor patient advocacy groups, the Fede legislation, and The Joint Commis

50. **Aggressive Sales Force:** Teva and A

which was incentivized to target doctor's offices an

increasing the number of people exposed to opioids

misleading messages detailed.

51. Teva and Allergan use a host of proven strategies to influence doctor prescribing, including but not limited to: a lucrative bonus system, sophisticated databases to target doctors who are already prolific prescribers with a large population of pain patients, intensive sales training to provide specific language for how to talk to prescribers, speakers' bureaus to disseminate promotional messaging to large groups of doctors all at once, free

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DECLARATION OF ANNA LEMBKE, M.D.
3:18-cv-07591-CRB

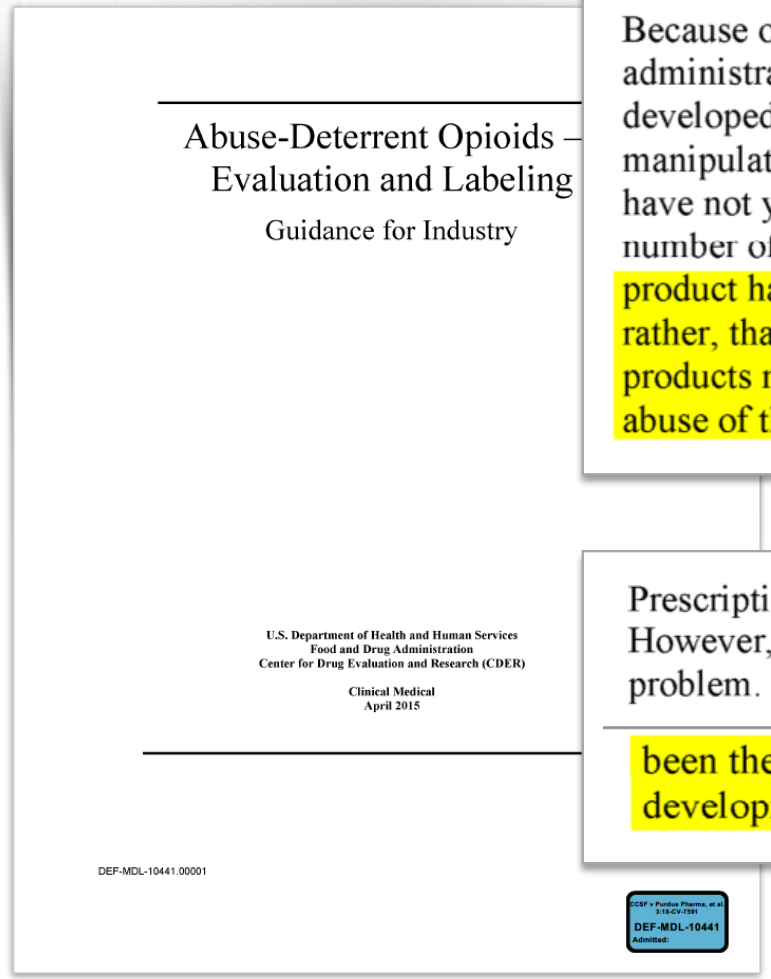
M. Misrepresentation #7: Abuse Deterrent Formulations decrease risk and addiction.

Teva Example:

- Teva's 2015 "Pain Matters" campaign conveyed messages that "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." **P-18318** (Speaker video presentation); **P-25414_00006** (script).

Lemke Decl. ¶ 48

FDA Guidance: Abuse-Deterrent Opioids (2015)



Because opioid products are often manipulated for purposes of abuse by different routes of administration or to defeat extended-release (ER) properties, most abuse-deterrent technologies developed to date are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. It should be noted that these technologies have not yet proven successful at deterring the most common form of abuse—swallowing a number of intact capsules or tablets to achieve a feeling of euphoria. Moreover, the fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties. Because opioid products must in the end be able to deliver the opioid to the patient, there may always be some abuse of these products.

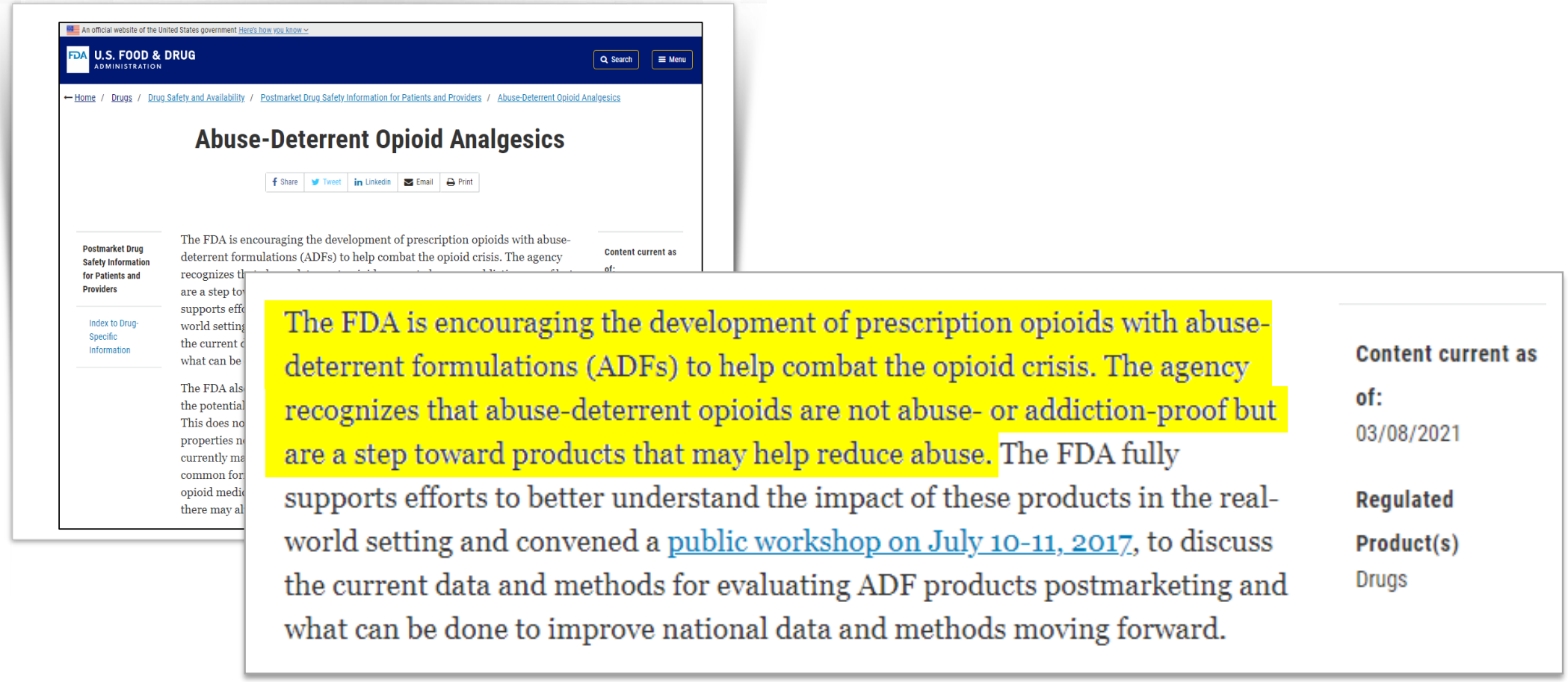
DEF-MDL-10441.00005

Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.

DEF-MDL-10441.00004-5

TCA Defendants Court Exhibit 00001.00055

Current FDA Website: Abuse-Deterrent Opioids

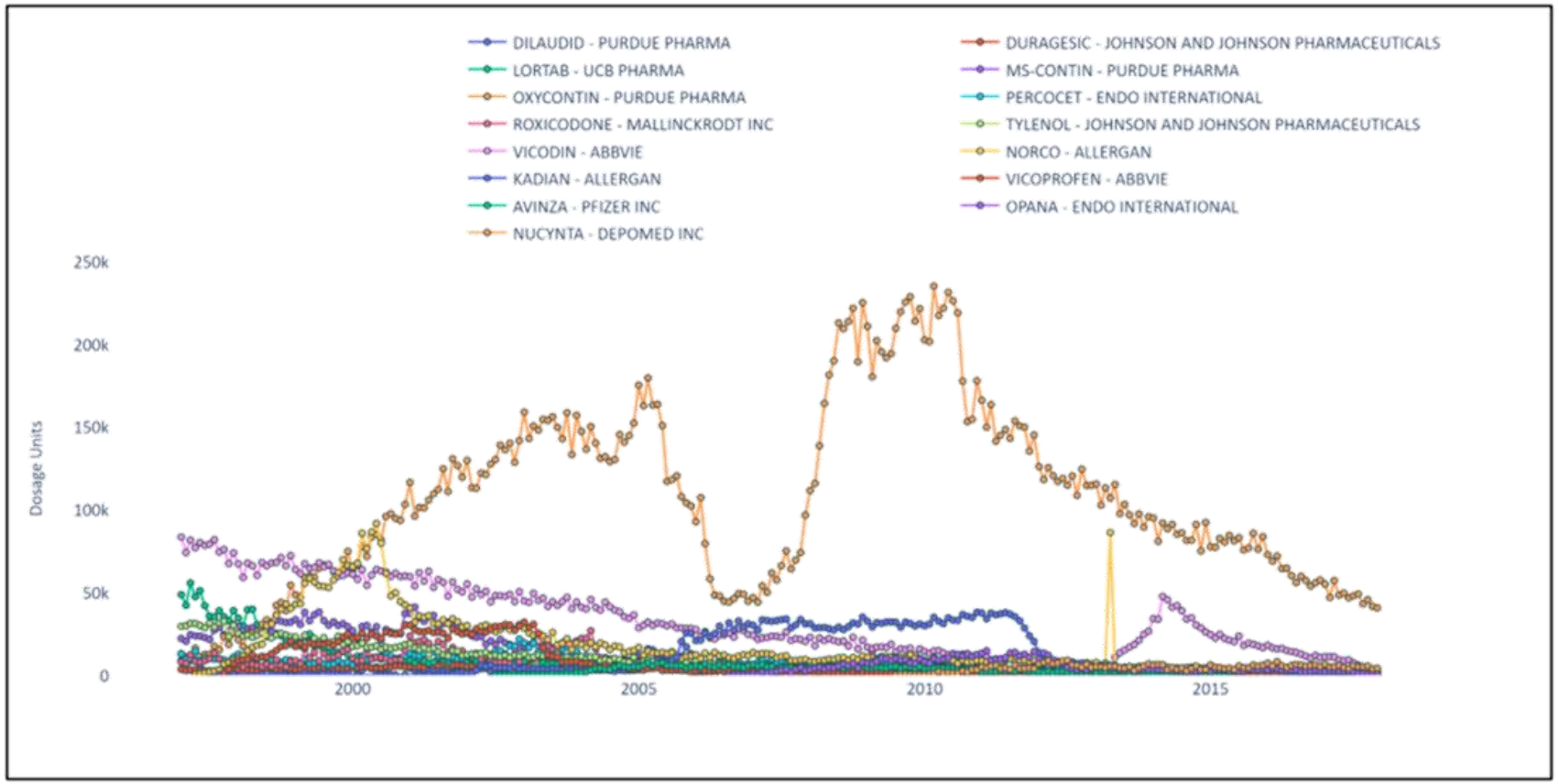


DEF-MDL-15949; DEF-MDL-05612

Lacey Keller's 15 Most Prescribed Branded Opioids

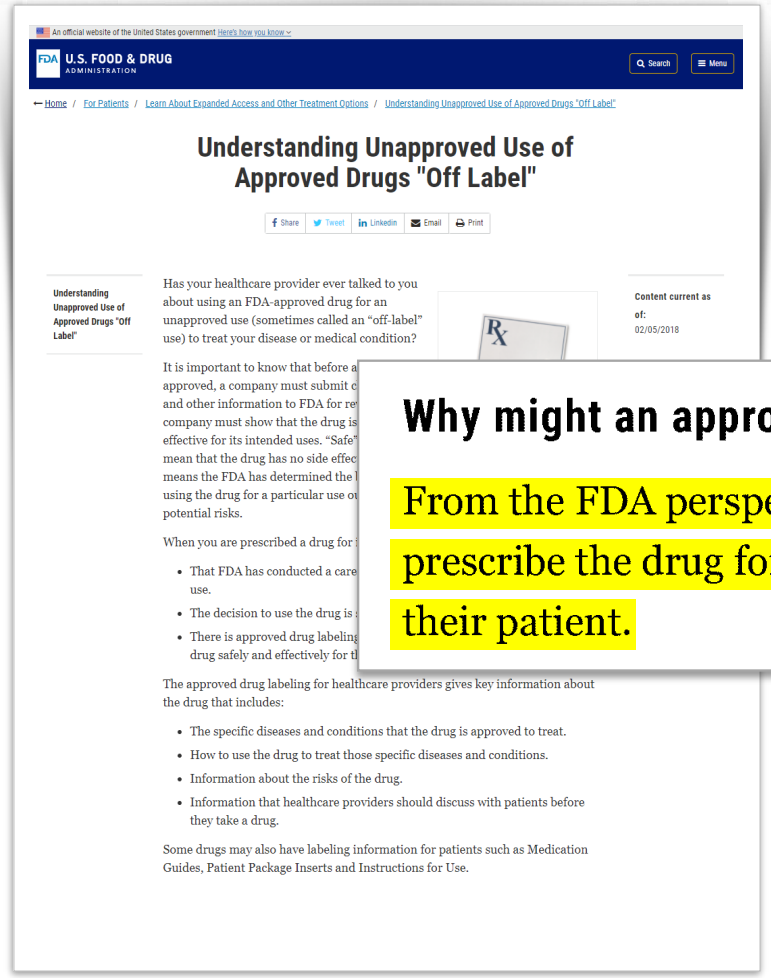
Figure 4: Prescriptions by Selected Drug Product Over Time
(IQVIA Xponent®: San Francisco County, 1997-2017)

The figure displays data for the fifteen most prescribed branded opioids.[26]



Plaintiff's Expert Keller Report, Fig. 4

FDA Policy Regarding Off-Label Prescriptions



An official website of the United States government Here's how you know

U.S. FOOD & DRUG ADMINISTRATION

Search Menu

Home / For Patients / Learn About Expanded Access and Other Treatment Options / Understanding Unapproved Use of Approved Drugs "Off Label"

Understanding Unapproved Use of Approved Drugs "Off Label"

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Understanding Unapproved Use of Approved Drugs "Off Label"

Has your healthcare provider ever talked to you about using an FDA-approved drug for an unapproved use (sometimes called an "off-label" use) to treat your disease or medical condition?

Content current as of: 02/05/2018

It is important to know that before a approved, a company must submit c and other information to FDA for re company must show that the drug is effective for its intended uses. "Safe" mean that the drug has no side effec means the FDA has determined the using the drug for a particular use ou potential risks.

When you are prescribed a drug for

- That FDA has conducted a care use.
- The decision to use the drug is
- There is approved drug labeling drug safely and effectively for t

The approved drug labeling for healthcare providers gives key information about the drug that includes:

- The specific diseases and conditions that the drug is approved to treat.
- How to use the drug to treat those specific diseases and conditions.
- Information about the risks of the drug.
- Information that healthcare providers should discuss with patients before they take a drug.

Some drugs may also have labeling information for patients such as Medication Guides, Patient Package Inserts and Instructions for Use.

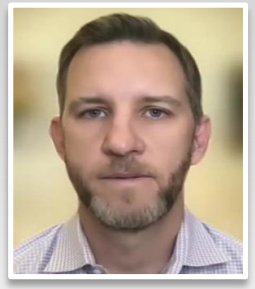
Current Policy

Why might an approved drug be used for an unapproved use?

From the FDA perspective, once the FDA approves a drug, healthcare providers generally may prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient.

TE-SF-02618.00002

San Francisco Area Sales Representative Testimony: No Off-Label Promotion



Tim Fortescue
(Cephalon Sales Representative)

Q Did you ever promote Actiq to a prescriber for off-label use?
MR. CRAWFORD: Objection.
THE WITNESS: No.
BY MR. HILL:
Q Did you ever promote Fentora to a prescriber for off-label use?
MR. CRAWFORD: Objection.
THE WITNESS: No.

* * *

Q Mr. Fortescue, were you ever encouraged by anyone at Cephalon to promote Actiq or Fentora for off-label use?
MR. CRAWFORD: Objection.
THE WITNESS: No.

12/1/2021, Dep. Tr. at 354:25-355:8, 21-25

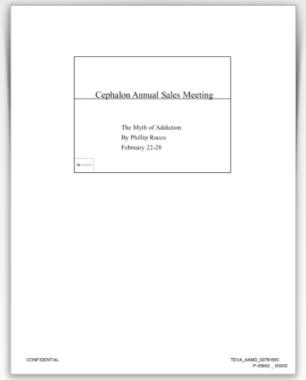
TCA Defendants Court Exhibit 00001.00059

Documents Containing "Misrepresentations"

Cephalon

Fentora Learning System Pre-module (2008)

P-24979_00002



Email attachment: "Cephalon Annual Sales Meeting" (2005)

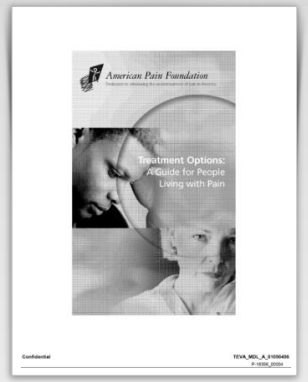
P-09992_00005

Teva USA

Pain Matters Script (2015)

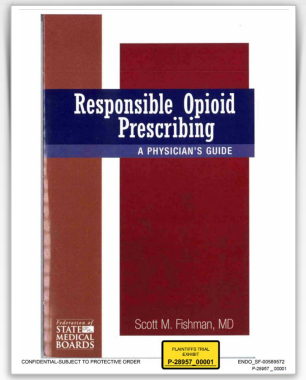
P-25414_00001

Other



Treatment Options: A Guide for People Living with Pain (2007)

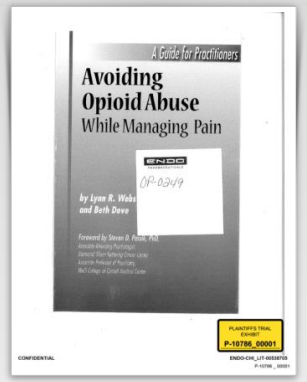
P-18356_00004



Responsible Opioid Prescribing (2007)

P-28957_00001

No Relation



Lynn Webster, "Avoiding Opioid Abuse While Managing Pain (2007)

P-10786