



Background and Rationale for the Development of Opioid-Sparing and Opioid-Replacement Drugs

Meeting of the Anesthetic and Analgesic Drug Products
Advisory Committee (AADPAC)
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Overview

Objective: To provide the committee with a framework for understanding the potential public health benefits of opioid-sparing drugs

- Prescription opioids and overdose death
- Recent guidelines and “one-size-fits-all” policies
- Changes in opioid analgesic prescribing and opportunities for further improvement
- Leftover medications and the potential for misuse



Prescription Opioids and Overdose Death

Drugs Involved in U.S. Overdose Deaths, 1999 to 2017

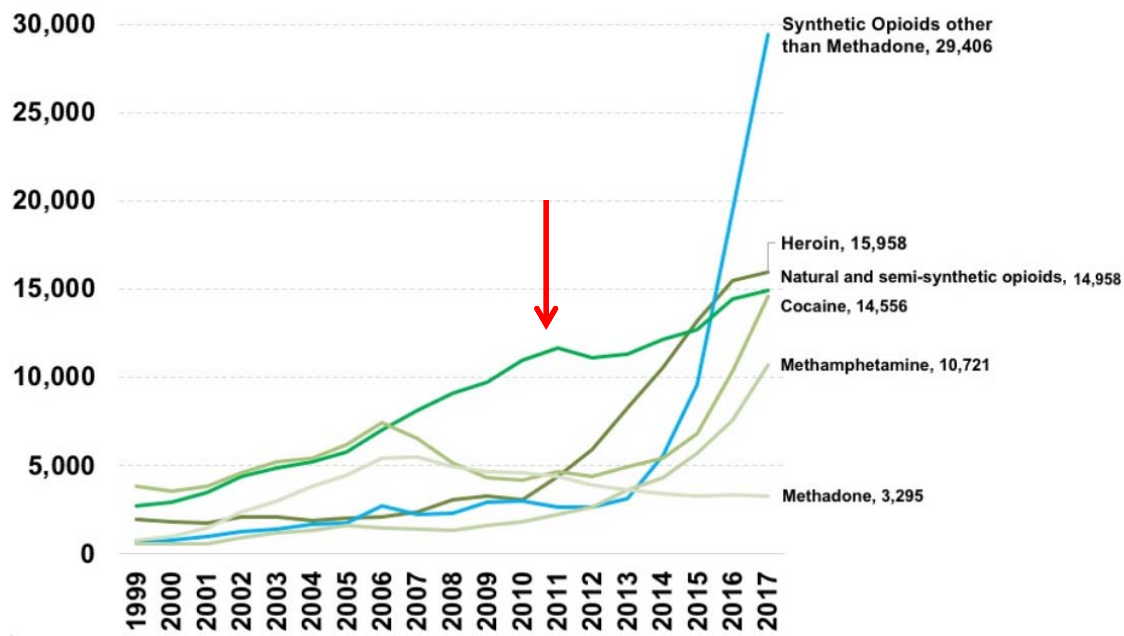


Figure Source: National Institute on Drug Abuse Data Source: CDC Wonder

Available from: <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>



Major Guidelines

- Interagency Guideline on Prescribing Opioids for Pain (Washington State Agency Medical Directors Group) (2015)
- CDC Guideline on Prescribing for Chronic Pain (2016)
- Michigan Opioid Prescribing Engagement Network* (2018)
- Johns Hopkins Post-Surgical Pain Management Guidelines* (2018)

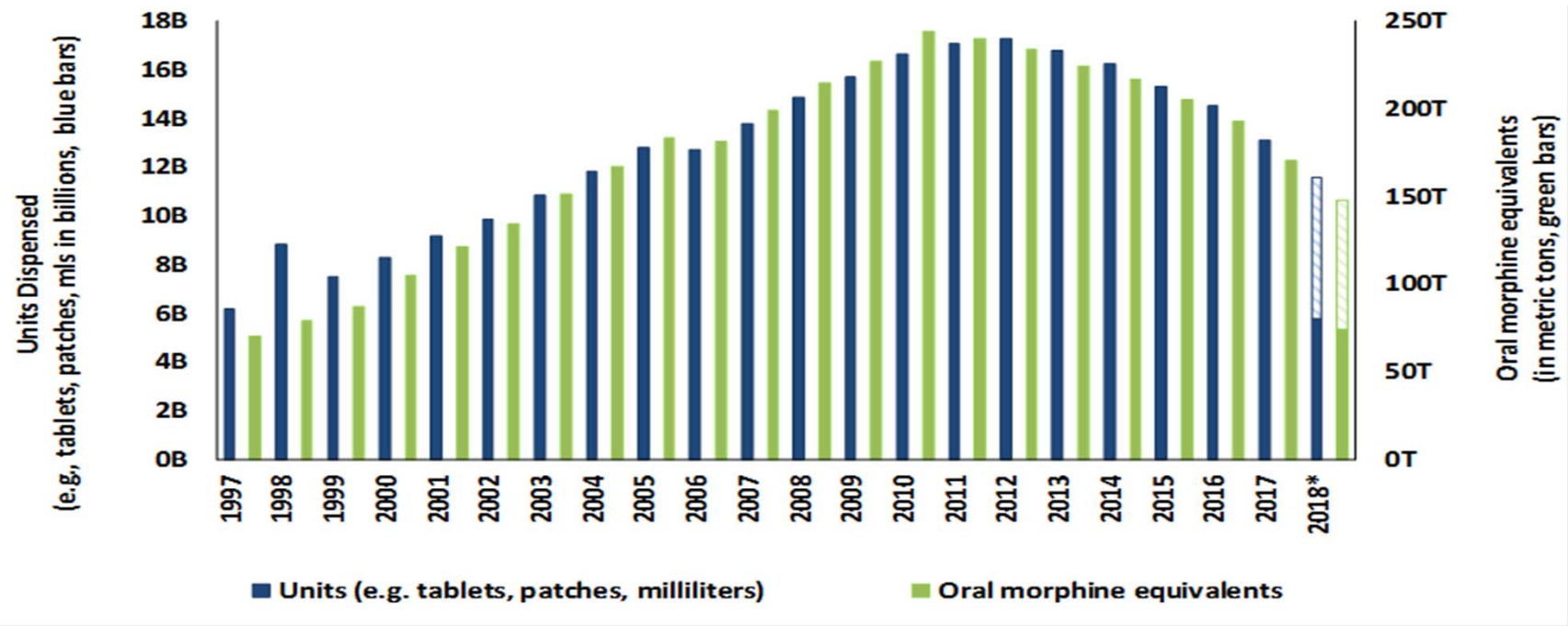
*Surgery-specific

Opioid Reduction Strategies: “One-size-fits-all”



- >20 states passed laws limiting initial prescription durations (e.g., 3-7 days), some with mandatory education
- DEA proposes decreasing manufacturing quotas by 10% for most frequently misused prescription opioids
- Oregon Medicaid proposes tapering chronic pain patients to doses of zero beginning in 2020 (2018)
- **Such policies**
 - do not account for variation in patients, conditions, or reasons for use
 - may lead to inadequate treatment of pain or other negative unintended consequences
 - create a pressing need to expand options for the treatment of acute and chronic pain

Opioid Analgesic Prescription Data

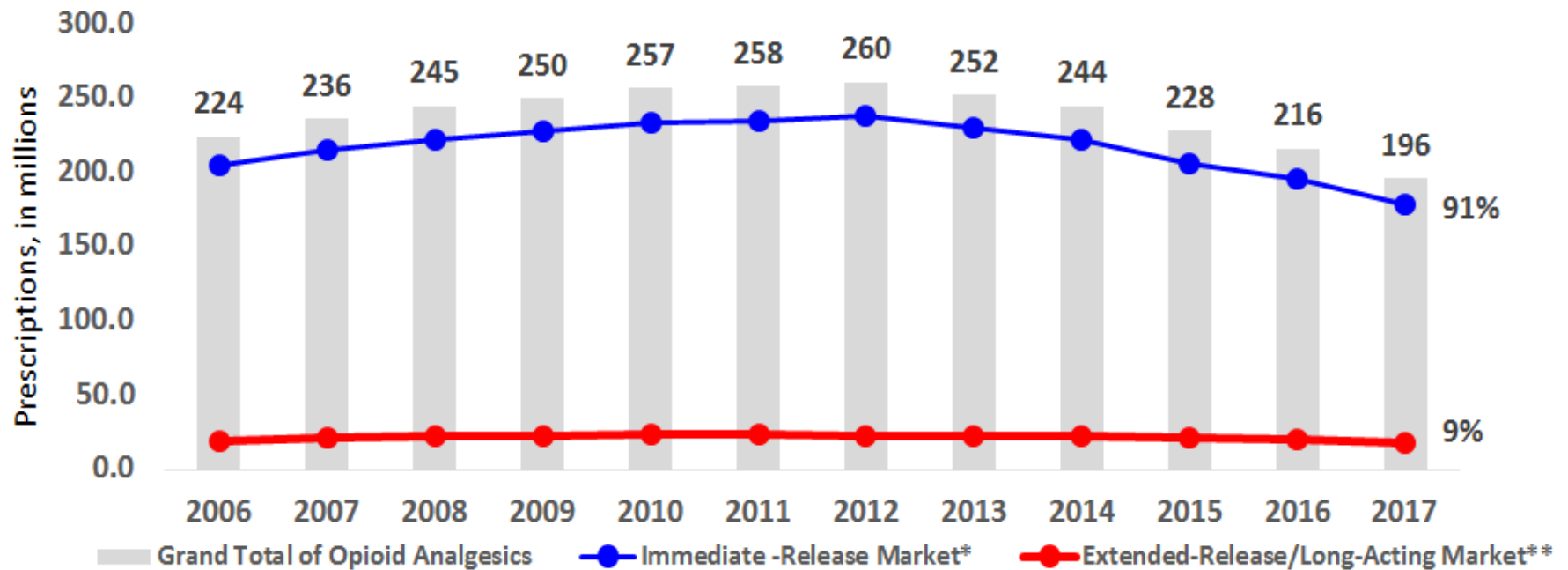


Source: IQVIA, National Prescription Audit™. 1997-June 2018.

One billion MME is equivalent to 1 metric ton of oral morphine equivalent

*Projected year 2018 based on doubling the number of units and oral morphine equivalents dispensed during the first half of 2018

Opioid Analgesic Prescription Data



Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2017. Static data extracted March 2017 and 2012-2017 data extracted February 2018.

*Immediate-Release formulations include oral solids, oral liquids, rectal, nasal, and transmucosal

**Extended-Release/Long-Acting formulations include oral solids and transdermal patches

Note: Include opioid analgesics only, excluding injectable formulations as well as opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products

“In Search of More Rational Prescribing”



“We’re now faced with the urgent need to craft policies that rationalize prescribing, and set a new and more appropriate medical standard for the use of opioids. At the same time, we will take heed that the drugs work, and there will be patients who need these medicines; for example, for the management of severe pain. In some medical circumstances opioids are the only drugs that work for some patients, such as those with metastatic cancer.”

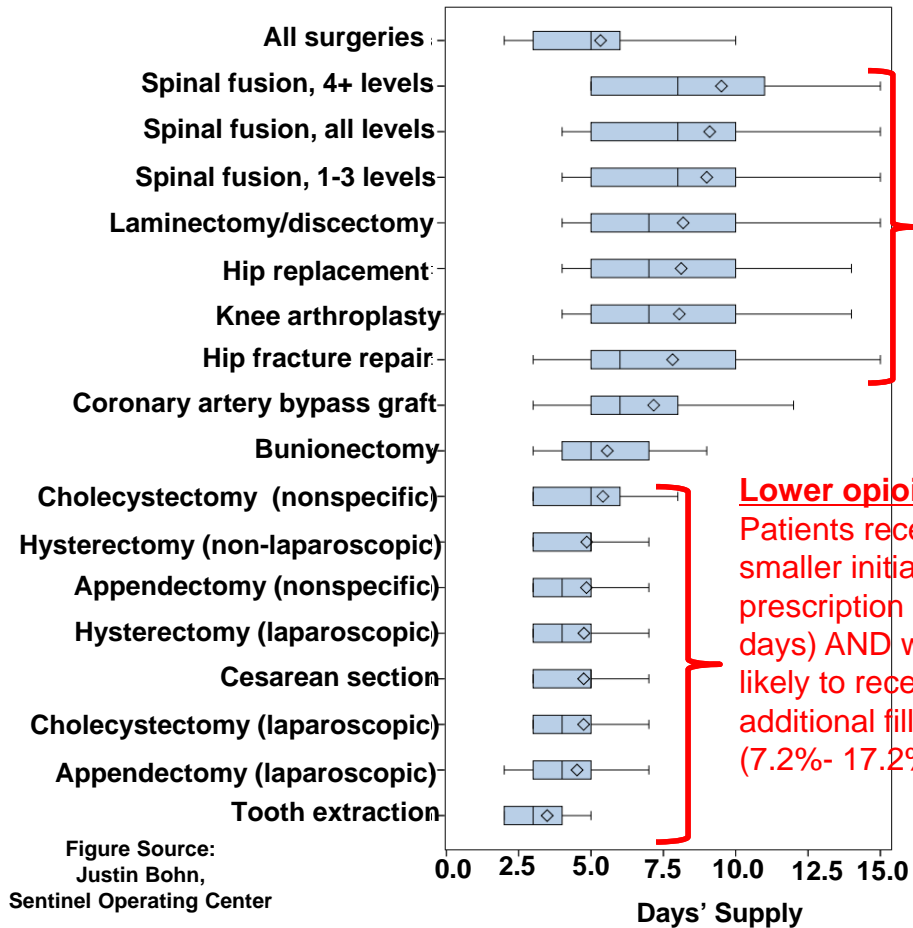
“I want to talk about some of the strategies FDA is pursuing to address these challenges; to reduce overall exposure to opioids, while preserving access for those patients who will benefit.”

Speech by Scott Gottlieb, M.D.
Commissioner of Food and Drugs
National Rx Drug Abuse and Heroin Summit
Atlanta, GA
April 4, 2018

FDA Study, Post-Surgical Opioid Use



- Sentinel Distributed Database 2009-2015 (prior to widespread implementation of prescribing limits)
- Commonly performed inpatient/outpatient surgical procedures (general, orthopedic, gynecologic, neurosurgical, thoracic)
- Descriptive analysis: % filling opioids after surgeries, and characteristics of initial prescriptions
- Models generated for “refill” rates (among individuals filling prescriptions for opioids) vs. initial days’ supplied



Higher opioid “need”
 Patients received larger initial prescriptions (median 6-8 days) AND were more likely to receive additional fills (17.2%- 61.4%)

Lower opioid “need”
 Patients received smaller initial prescription (median 3-5 days) AND were less likely to receive additional fills (7.2%- 17.2%)

*distributions in boxplot extend from 10th to 90th percentile; vertical line represents median, diamond represents means

Literature: Range in Consumption, by Surgery

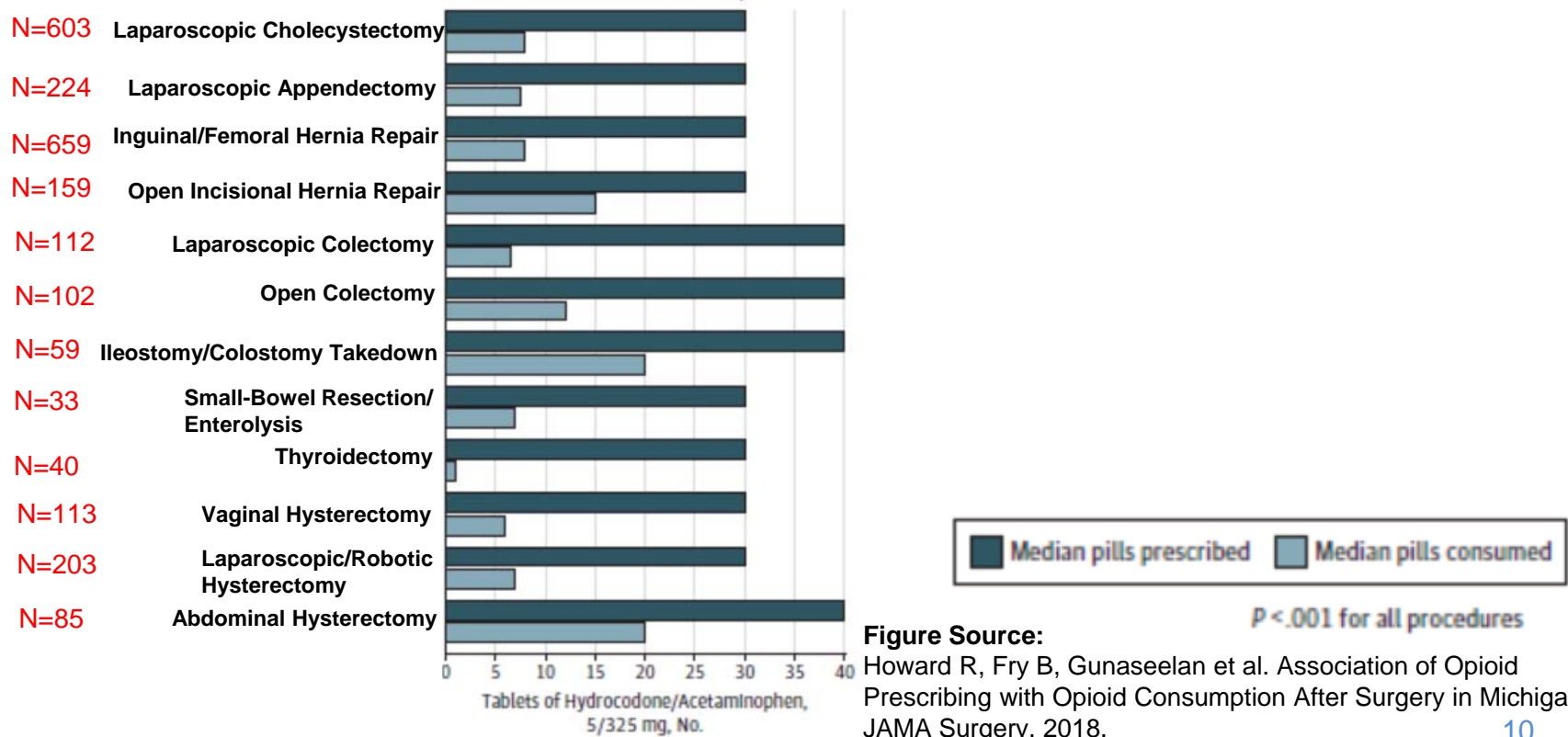
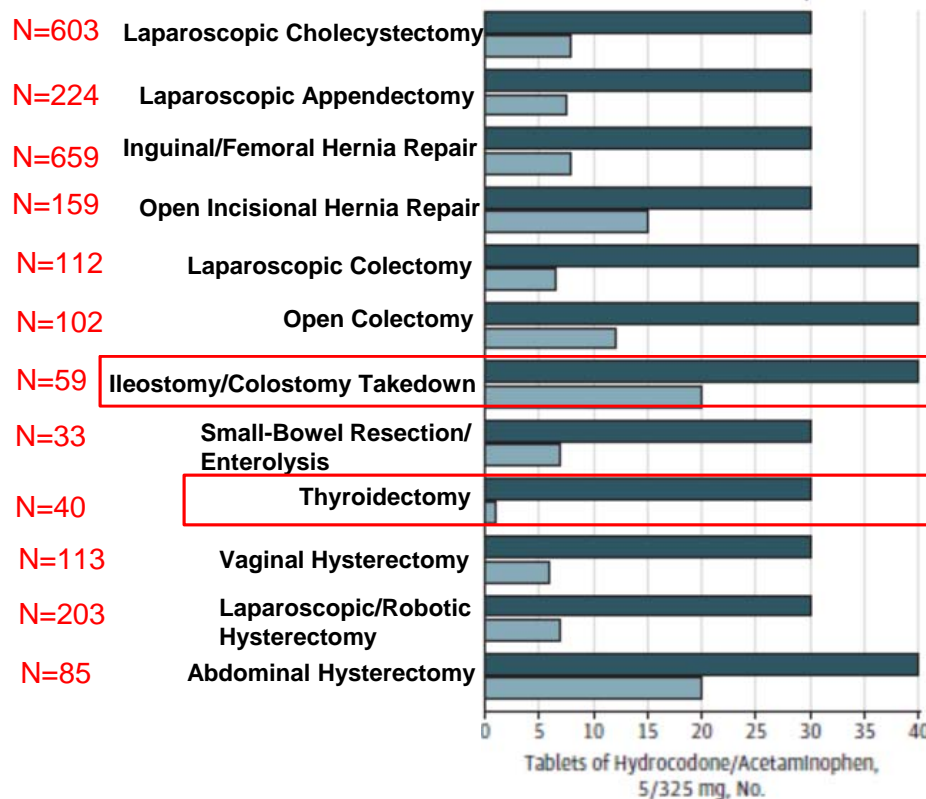


Figure Source:
 Howard R, Fry B, Gunaseelan et al. Association of Opioid Prescribing with Opioid Consumption After Surgery in Michigan. JAMA Surgery, 2018.

Literature: Range in Consumption, by Surgery



Median opioid consumption ranged from 3-67% of prescribed quantity

24% of patients overall took no opioids after surgery



$P < .001$ for all procedures

Figure Source: Howard R, Fry B, Gunaseelan et al. Association of Opioid Prescribing with Opioid Consumption After Surgery in Michigan. JAMA Surgery, 2018.

Literature: Leftover Supplies Following Surgery



Surgery	Number of Surgeries	Median Pills Prescribed*	Leftover Pills** (Median (IQR))	Total Leftover Pills
Laparoscopic cholecystectomy	603	30	18 (5-28)	10636
Laparoscopic appendectomy	224	30	20 (5-29)	4154
Vaginal hysterectomy	113	30	19 (5-27)	1870
Laparoscopic/ Robotic hysterectomy	203	30	20 (5-30)	3804
Abdominal hysterectomy	85	40	15 (0-30)	1383

*IQR not reported

**estimated in tablets of hydrocodone/acetaminophen 5/325 mg, derived from total oral morphine equivalents

Data Source: Howard R, Fry B, Gunaseelan et al. Association of Opioid Prescribing with Opioid Consumption After Surgery in Michigan. JAMA Surgery, 2018.

Literature: Leftover Supplies Following Surgery

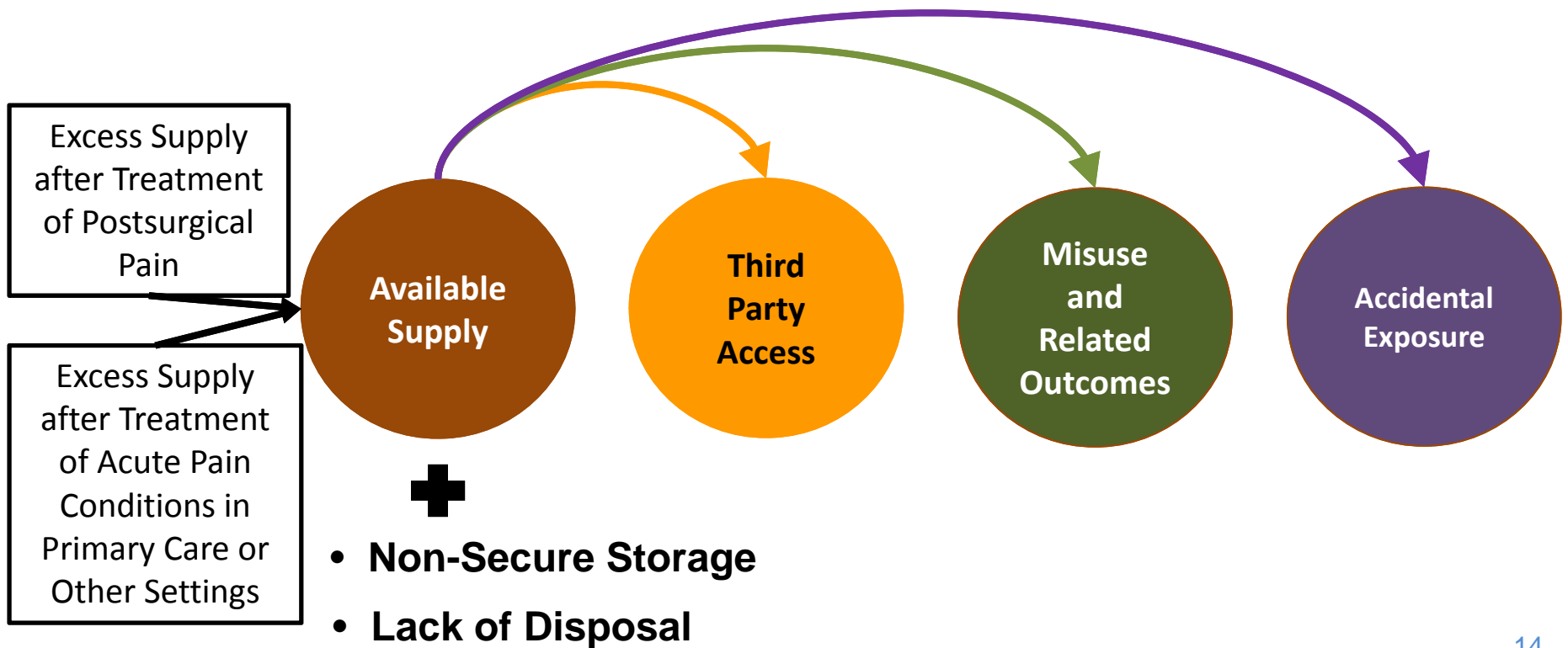


Procedure	Mean/ (range) tablets filled	Mean/Median tablets consumed	~Days required	~Leftover tablets
Total Knee Arthroplasty	74 (20-300)	n.d.; (35% required refills)	>14	n.d.
Outpatient Shoulder Surgery	60 (n.d.)*	37 (n.d.)*	9-10	23
Cesarean Delivery	40 (5-80)*	20*	4-5	20
Tooth Extraction	28 (n.d.)	13	2-3	15
Upper Extremity Surgery	30 (n.d.)	14 (Bone); 9 (Soft Tissue)	2-3	15
Laparoscopic Cholecystectomy	30 (0-100)	10-12	2-3	20
Laparoscopic Appendectomy	30 (n.d.)*	12*	2-3	18
Partial Mastectomy with Node Biopsy	23 (0-60)	6	1-2	17
Laparoscopic Inguinal Hernia Repair	33 (15-70)	9	1-2	24
Open Inguinal Hernia Repair	30 (15-120)	9	1-2	21
Partial Mastectomy	21 (0-50)	3	1	18
Dermatologic Surgery	9 (3-20)	4	1	5

n.d.=no data * Median number of tablets

Sources: Hill, et al., *Ann Surg*, 2017; Bateman, et al., *Obstet Gyn*, 2017; Maughan, et al., *Drug Alc Dep*, 2016.; Harris, et al., *JAMA Dermatol*. 2013; Bockman, et al. *J Pain*, 2017 (Abstract); Rogers, et al., *J Hand Surg*, 2012; Kumar, et al. *AJSM*, 2017; Bartels, 2016; Hernandez, 2017 ; Tan, 2017; Brummett, 2017

Risks of Leftover Opioid Analgesics



Sources of Misused* Pain Relievers

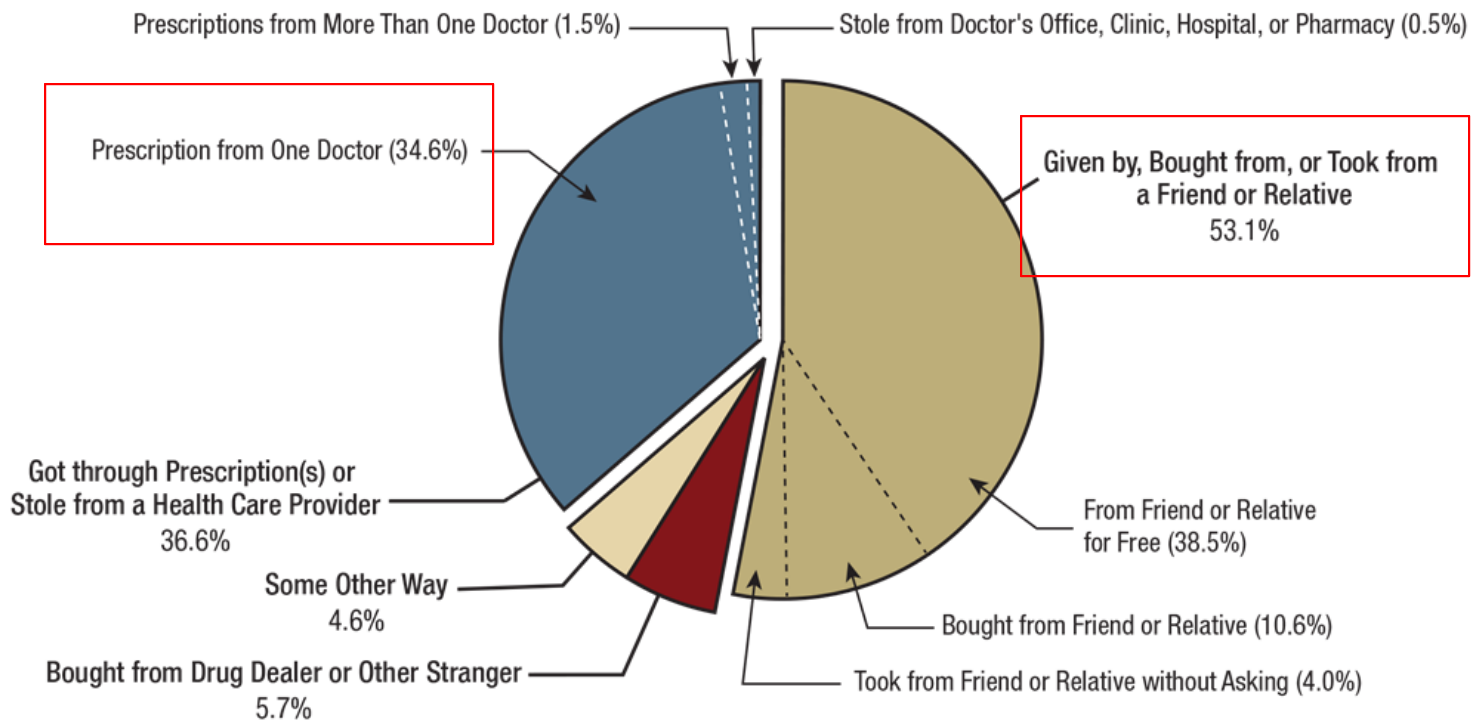


Figure Source: National Survey on Drug Use and Health (NSDUH), 2017

*NSDUH definition of "misuse" encompasses use of a drug in any mode other than as medically directed, including but not limited to abuse

Reasons for Pain Reliever Misuse*

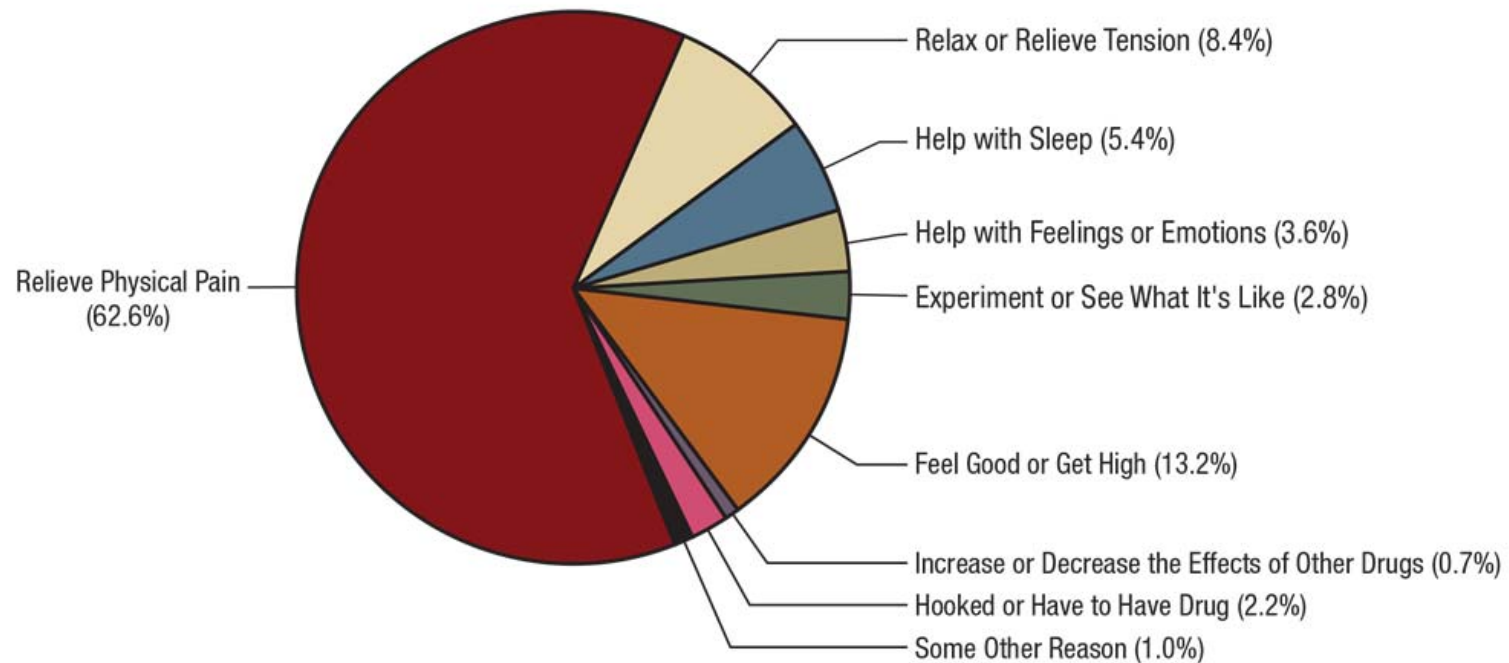


Figure Source: National Survey on Drug Use and Health (NSDUH), 2017

*NSDUH definition of "misuse" encompasses use of a drug in any mode other than as medically directed, including but not limited to abuse



Summary

Objective: To provide the committee with a framework for understanding the potential public health benefits of opioid-sparing drugs

- Guidelines and policies related to opioid prescribing may unintentionally restrict opioid access for patients in need
There is an urgent need to fill a rapidly growing void in pain management
- Recent trends in opioid prescribing suggest some reduction in prescribing levels
Further reductions are required for clinical settings where overprescribing still occurs
- Leftover medications are a major problem in the post-surgical setting with the potential for future misuse of prescription opioids by patients themselves or friends/family
By decreasing leftover opioid analgesics, use of opioid sparing alternatives may have a significant impact on opioid misuse in the overall population
- Overdose deaths involving prescription opioids continue to rise
With use of opioid-sparing drugs, a portion of these deaths may be averted



Conclusions

- Opioids are associated with serious risks of misuse, abuse, addiction and overdose
- Opioid sparing alternatives could be of great public health benefit by expanding safe and effective options in pain management while simultaneously helping to reduce the public health burden from adverse outcomes related to prescribed opioids



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Study Designs and Approved Product Labeling Relevant to Opioid Sparing

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AADPAC Meeting

November 15, 2018

What is Meant by Opioid Sparing?

- Decreasing the amount of opioid taken for analgesia while achieving comparable analgesic benefit
- Replacing opioids completely or in a certain setting (inpatient, outpatient)



Outline

- The Past
 - Recent, Relevant Published Studies (2016-2018)
 - Key Study Features
 - Approved products
 - Key Study Features
 - Findings and Labeling
 - Approved Products Designed to Mitigate Opioid-Related Adverse Reactions
- Issues to Consider Going Forward
 - Key Outcome Measures
 - Differences in Opioid Use
 - Opioid-Related Adverse Reactions
 - Study Design and Analgesic Rescue
 - Potential Impact of Development and Description in Labeling



Relevant Publications 2016-18



Features of Published Studies

- Surgery patients
- Were not designed to manage pain without an opioid
- All used quantitative measures of opioids as an outcome
- Most had no planned safety-related outcome

Interventions Studied in Publications

- Local anesthetic block
- Multimodal analgesia
- Non-steroidal anti-inflammatory drug (NSAID)
- Alpha-2 adrenergic agonist
- Gabapentinoid
- Muscle relaxant

Publications



Author/Year	Intervention	Placebo Control	Opioid Rescue	Opioid- Related Adverse Events
Purdy/2018	levobupivicaine		X	
Reagan/2017	multimodal		X	
Argoff/2016	diclofenac	X	X	
Bang/2016	bupivicaine	X	X	
Zhao/2016	dexmedetomidine	X	X	
Cai/2016	dexmedetomidine	X	X	
Sousa/2016	MgSO4	X	X	X
Ahn/2016	pregabalin	X	X	X
Li/2016	parecoxib	X	X	X
Chan/2016	dexmedetomidine	X	X	
Bakshi/2016	bupivicaine	X	X	
Jin/2016	nefopam	X	X	



Approved Products for Acute Pain with Relevant Labeling



Products

Trade name	Established name	Study Population
Ofirmev	acetaminophen injection	Total hip or knee arthroplasty
Exparel	bupivacaine injection	Total shoulder or rotator cuff repair, bunionectomy, hemorrhoidectomy
Caldolor	ibuprofen injection	Abdominal hysterectomy
Sprix	ketorolac nasal spray	Abdominal or orthopedic surgery



Study Design

- Randomized
- Double-blind
- Placebo-controlled
- Parallel group
- Opioid available as rescue
- No standard-of-care add-on designs



Opioid Rescue Medication in Relevant Studies

- Morphine Patient Controlled Analgesia (PCA)
24-72 hours
- Morphine sulfate 10 mg IM q4h as needed
(PRN)
- Oxycodone 5-10 mg PO q4h as needed



Outcome Assessments in Relevant Studies

- Pain
 - Patient-reported pain intensity on a rating scale
- Opioid Use
 - Study staff recorded PCA or PRN opioid use during efficacy ascertainment period

Endpoints in Relevant Studies

- Primary efficacy
 - Summed pain intensity difference over 24 or 48 hours
 - Area under curve of pain intensity scores over 72 hours
- Opioid use
 - Mean mg opioid used
 - Difference in mean mg opioid used expressed as % of use in placebo group (36% less morphine use than placebo)
 - % subjects that used no opioid



Labeling of Relevant Studies

- All describe less consumption
 - by mean mg morphine-equivalent opioid or % less opioid
 - % subjects that were opioid-free
- Two out of four labels include caveat that clinical benefit of described findings was not demonstrated or not established



Difference in Morphine PCA Use

Product	Surgery type	Morphine PCA use
Ofirmev (acetaminophen)	Orthopedic surgery	Mean morphine consumption through 24 hours: 38 mg in Ofirmev and 57 mg in placebo
Caldolor (ibuprofen)	Abdominal hysterectomy	Mean morphine consumption through 24 hours: 47 mg in Caldolor group and 56 mg in placebo
Sprix (ketorolac)	Abdominal or orthopedic surgery	26% and 36% less morphine over 48 hours than placebo, mean morphine consumption through 24 hours: 42 mg in Sprix group vs. 54 mg in placebo and 38 mg in Sprix group vs. 56 mg in placebo



Not Described in Relevant Labels

- A reduction in opioid-related adverse reactions
- The number of patients who do not require opioid analgesics
 - more distal to surgery
 - based on clinical setting (inpatient, outpatient)

Other Products Describing Opioid Use in Labeling



Drug	Indication	Design	Endpoints	Relevant Labeling
Orilissa, elagolix tablet	Moderate to severe pain associated with endometriosis	Randomized, double blind, placebo-controlled, premenopausal women with endometriosis	Responder analysis requiring both a reduction in pain and not more than a 15% increase in rescue analgesic use (opioid/APAP or naproxen)	Table 13 summarizing proportion of patients who stopped opioid rescue at 3 and 6 months “The clinical relevance of these data has not been demonstrated.”
Zytiga, abiraterone acetate tablet	Metastatic castration-resistant prostate cancer and metastatic high-risk castration-sensitive prostate cancer	Randomized, placebo-controlled, prostate cancer patients not taking opioids	Overall survival and radiographic progression-free survival	“The median time to opiate use for prostate cancer pain was not reached for patients receiving ZYTIGA and was 23.7 months for patients receiving placebo (HR=0.686; 95% CI: [0.566, 0.833], p=0.0001). The time to opiate use result was supported by a delay in patient reported pain progression favoring the ZYTIGA arm.”



Products Indicated for Preventing or Reducing an Opioid-Related Adverse Reaction



Products with Opioid-Induced Constipation Indication

Trade name	Established name
Movantik	naloxegol
Relistor	methylnaltrexone
Symproic	naldemedine
Amitiza	lubiprostone



OIC Study Design

- Placebo-controlled studies
- Primary endpoint
 - proportion of responders
 - defined as ≥ 3 spontaneous bowel movements (SBMs) per week and change from baseline of ≥ 1 SBM per week for at least 9 of the 12 study weeks and 3 of the last 4 weeks

Products with Postoperative Nausea and Vomiting Indication



Trade name	Established name
Zofran	ondansetron
Zuplenz	ondansetron
Emend	aprepitant
Aloxi	palonosetron
Tigan	trimethobenzamide

PONV Study Design

- Placebo control, superiority or active control, noninferiority
- Primary endpoints
 - proportion of responders
 - defined as no vomiting or antiemetic rescue use in pre-specified time periods
 - 0-24 hours
 - 24-72 hours



The Future

Issues for consideration



Potential Value of Opioid Sparing

- Reducing unwanted direct physiologic effects
 - Respiratory depression
 - Nausea, vomiting, constipation
 - Dizziness, sedation
- Reducing risk of developing or exacerbating addiction and related behaviors in
 - Patients prescribed opioids
 - Those exposed to prescription opioids who were not prescribed the medication



Potential Unintended Consequences of Opioid Sparing

- Prescribing changes
 - Decreased analgesic benefit
 - Increased polypharmacy
 - New analgesic with abuse liability
- Prescribing of opioids does not change
 - More leftover opioids in medicine cabinets
- Labeled opioid-sparing effect does not confer benefits in actual clinical practice



Study Design



Replacement for Opioid

- Population for which opioid analgesia required
- Placebo-controlled trials
 - Superiority on efficacy
- Active-controlled trials -opioid comparator
 - Noninferiority on efficacy
- Compare proportion of patients not using rescue



Noninferiority Studies

- Noninferiority margin
- Larger sample size
- Assay sensitivity
 - If there is no difference between two active treatment groups, it may be because both treatments are successful in managing pain or because neither treatment was successful in managing pain

Reduction in Opioid Use



- Placebo-controlled trials
 - Superiority on pain
 - Superiority on opioid rescue
- Active-controlled trials
 - Superiority on opioid rescue
 - NI on pain
- Measure or do a formal comparison of clinically relevant reduction in opioid-related adverse reactions



Analgesic Rescue



Opioid Rescue Use

- Analgesic rescue can reduce assay sensitivity
- Opioid PCA can overshoot and not be correlated with pain scores
- Adequate rescue may be particularly challenging if trying to demonstrate that a product can be used in place of an opioid



Non-Opioid Analgesic Rescue

- NSAIDs (coxibs and tNSAIDs)
- Acetaminophen
- Local anesthetics
- NMDA receptor antagonists



Outcomes



Effects on Opioid Consumption

- Describe differences associated with a clinically important outcome
- Use a dichotomous outcome of opioid use
 - Inpatient use
 - Requirement for prescription at discharge
 - Outpatient use
- Describe the difference and allow prescribers to interpret its clinical importance

Opioid-Related Adverse Reactions

- Regulatory precedent for clinical significance
 - Nausea and vomiting
 - Constipation
- Other reactions of interest
 - Respiratory depression
 - Sedation
 - Dizziness
 - Urinary retention
 - Pruritus



Summary

- Studying and describing opioid-sparing outcomes have potential individual and societal benefits
- Differences in opioid consumption in studies that used a placebo control have been described in approved product labels
- There are precedents for defining a clinically meaningful effect on an opioid-related adverse reaction
- There are other potential study designs that are not represented in the precedents to date
- Unintended consequences should be considered