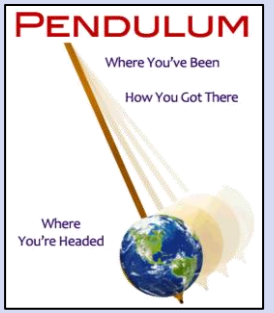


Opioid therapy for chronic pain: challenges, evidence & strategies

Gary Jay Brenner, MD, PhD

Director, MGH Pain Medicine Fellowship
Dept of Anesthesia, Critical Care & Pain Medicine
Massachusetts General Hospital

Associate Professor of Anesthesia
Harvard Medical School

Conflicts of Interest: none

Disclosures:

NIH STTR award (PI)

Founder/Equity - Mulberry Biotherapeutics

Learning Objectives

- Be aware of the societal consequences of prescription opioid utilization
- Review the data on efficacy and safety of opioid therapy for chronic pain
- Discuss a rational approach to using opioids for the treatment for chronic pain

Key Questions

- Can long-term opioid therapy reduce pain, support function, and improve QoL? (NNT)
- What are the risks of long-term opioid therapy? (NNH)

Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium.

Sir Thomas Sydenham,1680

ER hydrocodone (Hysingla™) – clinical trial efficacy data0

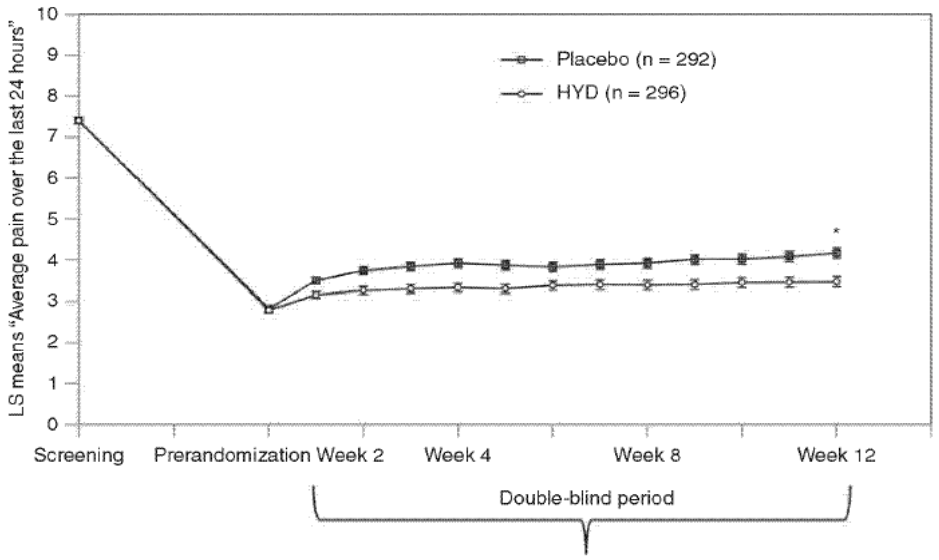
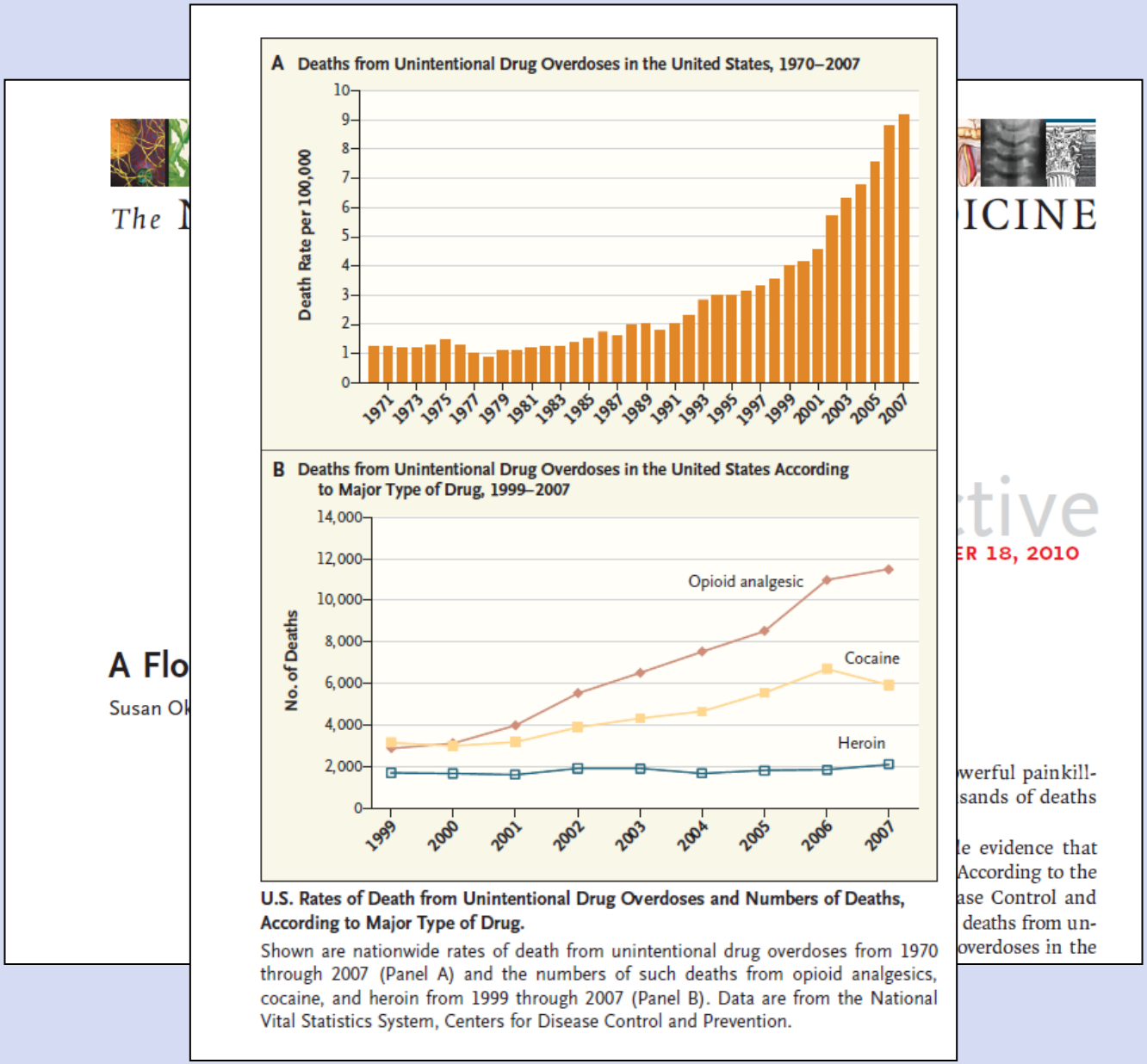


Figure 3. Primary endpoint throughout the study.
*p = 0.0016.

Wen et al., Exp Opin Pharm 2015

Societal Consequences of Prescription Opioids

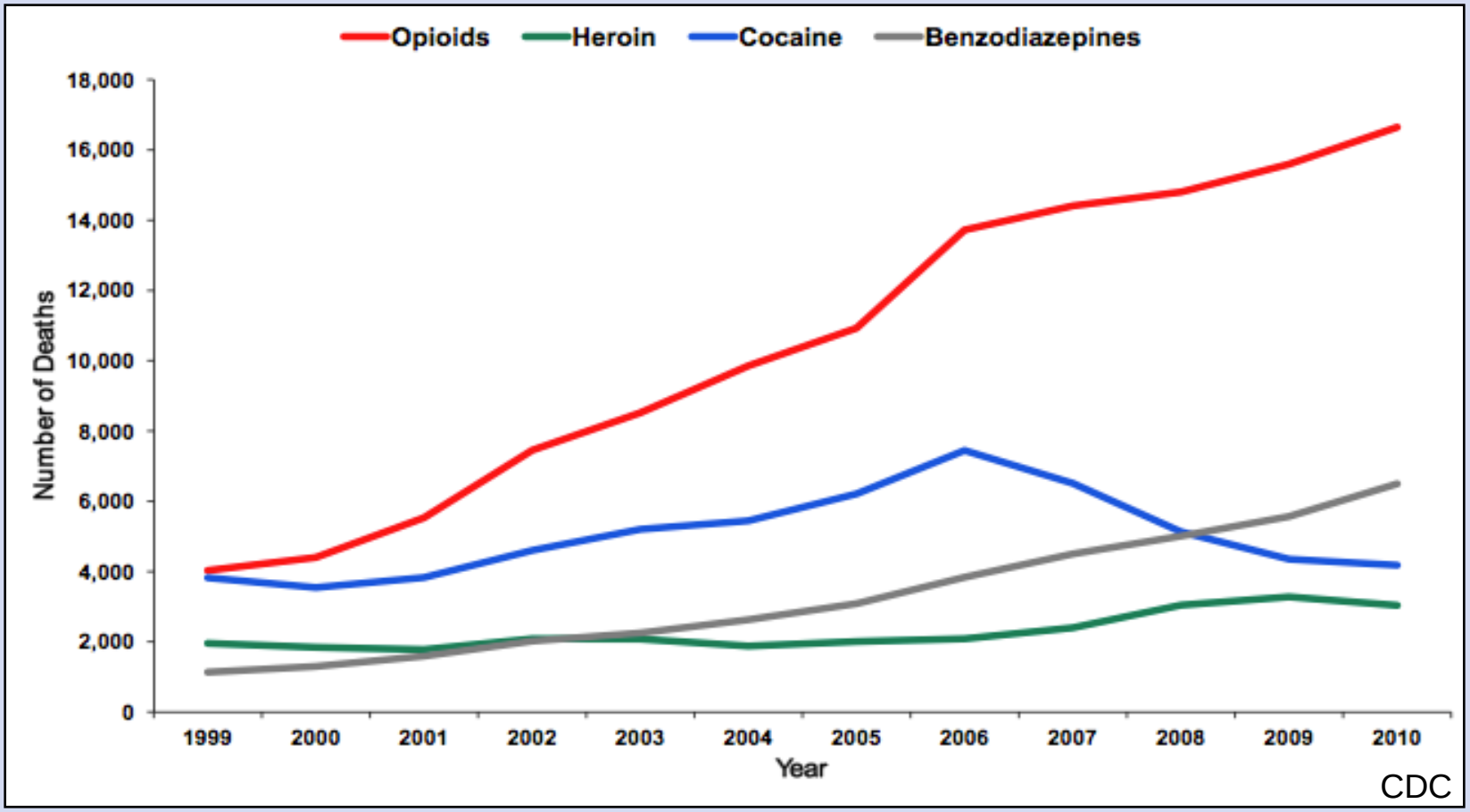
Opioid Misuse, Abuse & Death: A National ‘Epidemic’



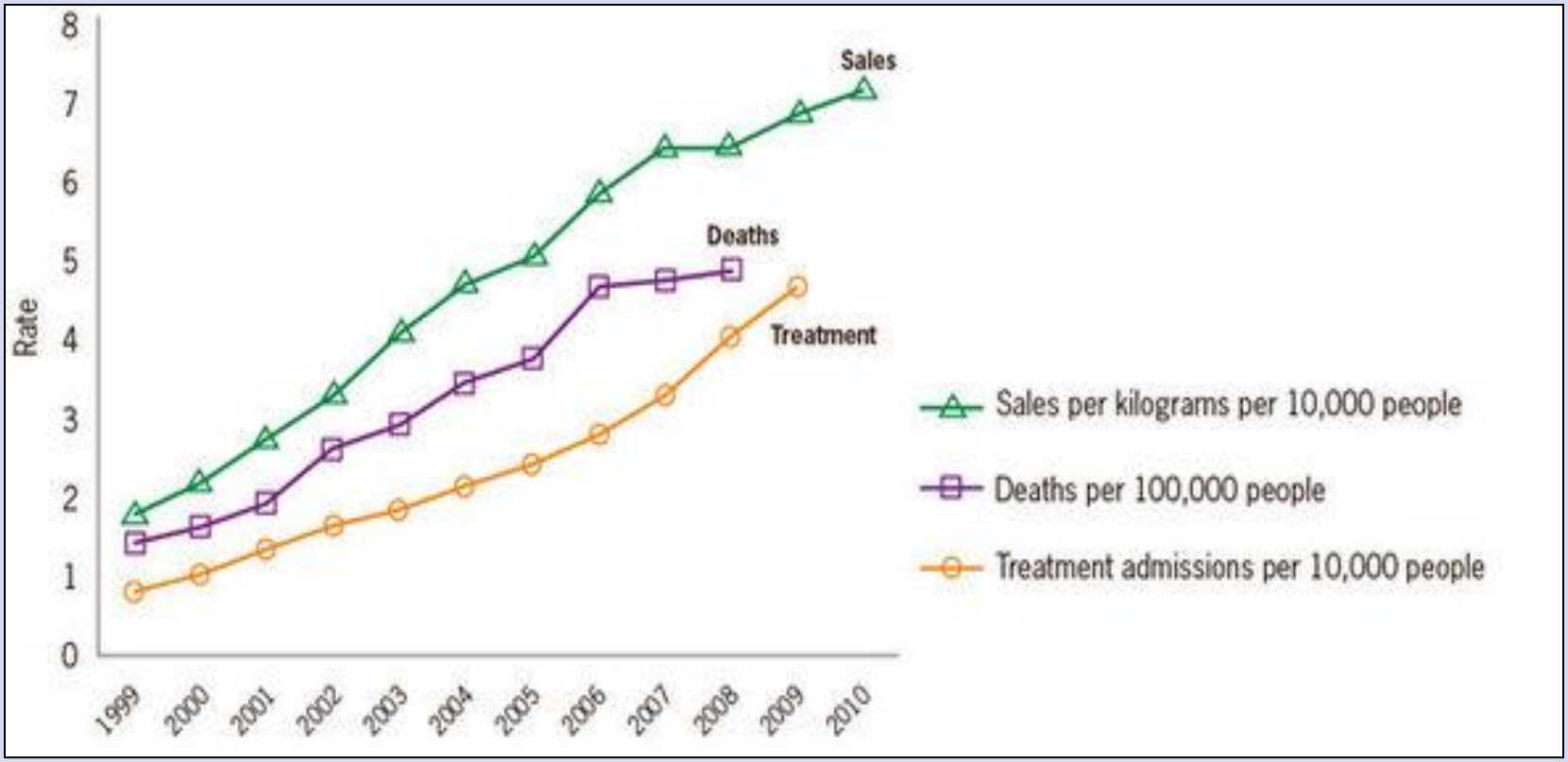
U.S. Rates of Death from Unintentional Drug Overdoses and Numbers of Deaths, According to Major Type of Drug.

Shown are nationwide rates of death from unintentional drug overdoses from 1970 through 2007 (Panel A) and the numbers of such deaths from opioid analgesics, cocaine, and heroin from 1999 through 2007 (Panel B). Data are from the National Vital Statistics System, Centers for Disease Control and Prevention.

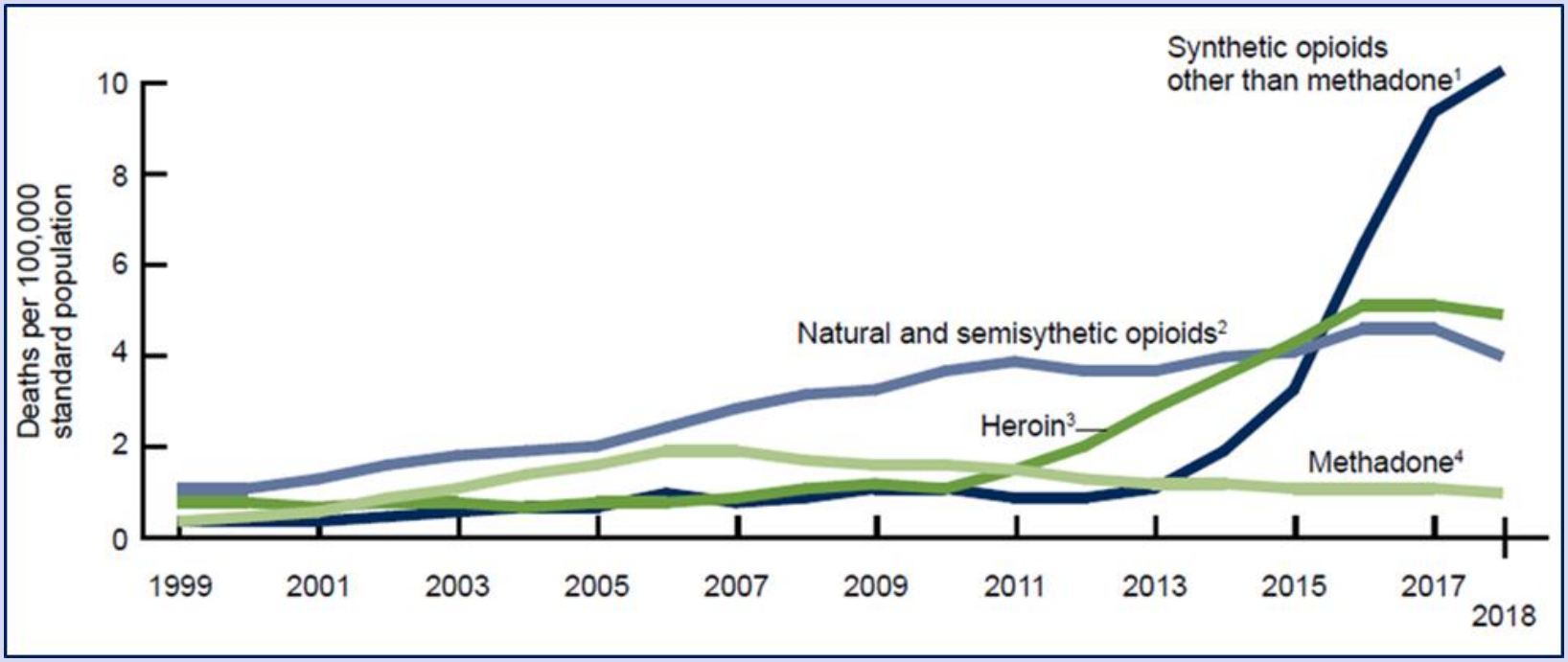
U.S. Unintentional Overdose Deaths



U.S. Opioid Sales, Treatment & Total Deaths

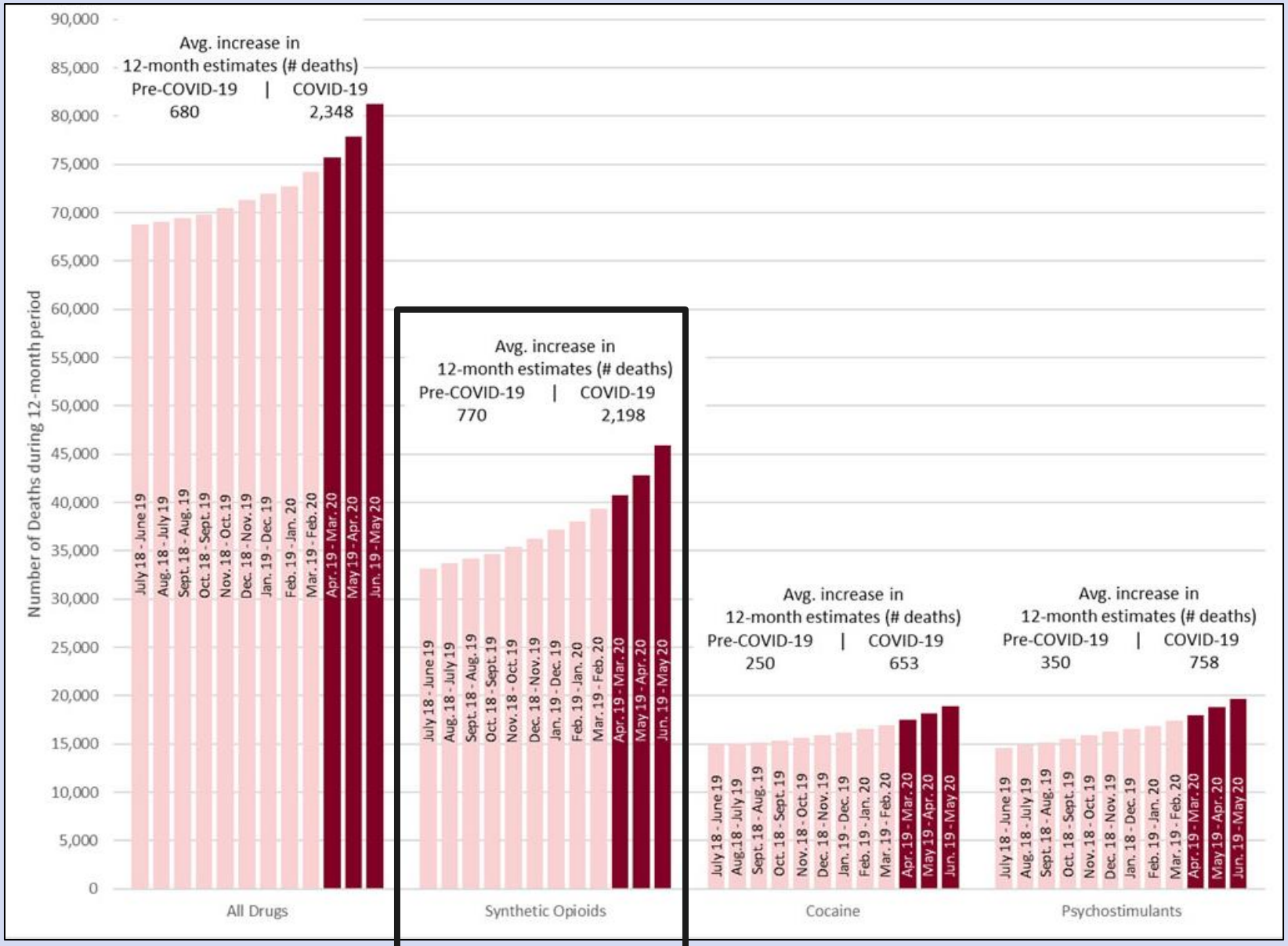


U.S. Overdose Deaths by Opioid Category (CDC)



Age-adjusted drug overdose death rates involving opioids, by type of opioid: USA 1999-2018 (https://www.cdc.gov/nchs/products/databriefs/db356.htm)

Drug Overdose Deaths (U.S.) – COVID-19



CDC Health Alert Network
December 17, 2020; CDCHAN-00438

Increased Opioid Prescribing (U.S.) – COVID-19

JAMA Network Open. 10 Dec. 2021

Original Investigation | Substance Use and Addiction

Substitution of Nonpharmacologic Therapy With Opioid Prescribing for Pain During the COVID-19 Pandemic

Byungkyu Lee, PhD; Kai-Cheng Yang, MS; Patrick Kaminski, MA; Siyun Peng, PhD; Meltem Odabas, PhD; Sumedha Gupta, PhD; Harold D. Green Jr, PhD; Yong-Yeol Ahn, PhD; Brea L. Perry, PhD

Abstract

IMPORTANCE During the pandemic, access to medical care unrelated to COVID-19 was limited because of concerns about viral spread and corresponding policies. It is critical to assess how these conditions affected modes of pain treatment, given the addiction risks of prescription opioids.

OBJECTIVE To assess the trends in opioid prescription and nonpharmacologic therapy (ie, physical therapy and complementary medicine) for pain management during the COVID-19 pandemic in 2020 compared with the patterns in 2019.

DESIGN, SETTING, AND PARTICIPANTS This retrospective, cross-sectional study used weekly claims data from 24 million US patients in a nationwide commercial insurance database (Optum's deidentified Clinformatics Data Mart Database) from January 1, 2019, to September 31, 2020. Among patients with diagnoses of limb, extremity, or joint pain, back pain, and neck pain for each week, patterns of treatment use were identified and evaluated. Data analysis was performed from April 1, 2021, to September 31, 2021.

MAIN OUTCOMES AND MEASURES The main outcomes of interest were weekly rates of opioid prescriptions, the strength and duration of related opioid prescriptions, and the use of nonpharmacologic therapy. Transition rates between different treatment options before the outbreak and during the early months of the pandemic were also assessed.

RESULTS A total of 21 430 339 patients (mean [SD] age, 48.6 [24.0] years; 10 960 507 [51.1%] female; 909 061 [4.2%] Asian, 1 688 690 [7.9%] Black, 2 276 075 [10.6%] Hispanic, 11 192 789 [52.2%] White, and 5 363 724 [25.0%] unknown) were enrolled during the first 3 quarters in 2019 and 20 759 788 (mean [SD] age, 47.0 [23.8] years; 10 695 690 [51.5%] female; 798 037 [3.8%] Asian; 1 508 023 [7.3%] Black, 1 976 248 [9.5%] Hispanic, 10 059 597 [48.5%] White, and 6 417 883

Key Points

Question Was nonpharmacologic therapy (ie, physical therapy and complementary medicine)—a low-risk alternative treatment for acute and chronic pain—replaced by prescription opioid analgesics during the COVID-19 pandemic?

Findings This cross-sectional study of weekly claims data from 24 million commercially insured patients in the US found evidence of substitution of nonpharmacologic therapy with increased opioid prescribing, accompanied by more potent and longer prescriptions, at the population and individual levels during the early months of the COVID-19 pandemic.

Meaning These findings suggest that progress toward reversing the opioid epidemic may have been stalled by the pandemic as practitioners resorted to higher levels of opioid prescribing to control pain in the absence of less risky alternatives.

Increased Opioid Prescribing - Causes

Pain treatment promoted aggressively since early 1990's:

- Patients and Patient Advocacy Groups (Pain "Bill of Rights")
- Medical Societies
- **Industry**

Prescription opioid use increased 10-fold 1990 to 2010:

- 1997-2002: Sales for oxycodone and methadone quadrupled.
- Extended-release formulations drove much of the growth.

Okie S. N Engl J Med 2010;363:1981-1985

Increased Opioid Prescribing - Causes

CLINICAL PHARMACOLOGY

ER oxycodone (OxyContin) Package Insert

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as 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

ER hydrocodone (Vantrela ER®) Package Insert (released Jan 2018)

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as 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.

POLITICS

U.S. Charges 412, Including Doctors, in $1.3 Billion Health Fraud

By REBECCA R. RUIZ JULY 13, 2017

Attorney General Jeff Ses
nationwide crackdown o

STORYLINE > ONE NATION OVERDOSED

HEALTH
ONE NATION OVERDOSED
OCT 26 2017, 6:13 PM ET

SHARE
Share
Tweet
Email
Print

Billionaire Charged With Bribing Doctors to Prescribe Opioids

by CYNTHIA MCFADDEN

The billionaire
with leading a
distribution of

Dr. John N. K
Insys and still
conspiracy to
addition to fin
sentences of
years.

Opioid executive John Kapoor sentenced to 5 and a half years in prison for bribing doctors to push fentanyl-based painkiller

By JOSEPH WILKINSON
NEW YORK DAILY NEWS | JAN 23, 2020 | 6:01 PM

Insys Therapeutics founder John Kapoor, right, departs federal court Thursday, Jan. 23, 2020, in Boston.(Charles Krupa/AP)

LATEST U.S.

Stimulus checks delayed after government insists on adding Trump's name: report
APR 14, 2020

California pastors sue Gov. Gavin Newsom over ban on religious services
APR 14, 2020

Justice Department throws support behind Mississippi church that defied local coronavirus order
APR 14, 2020

Ex-professor, plague expert in jail for alleged sex-murder fantasy, asked for release to help with coronavirus
APR 14, 2020

23 Nov. 2021

npr

SIGN IN NPR SHOP DONATE

NEWS ARTS & LIFE MUSIC PODCASTS & SHOWS SEARCH

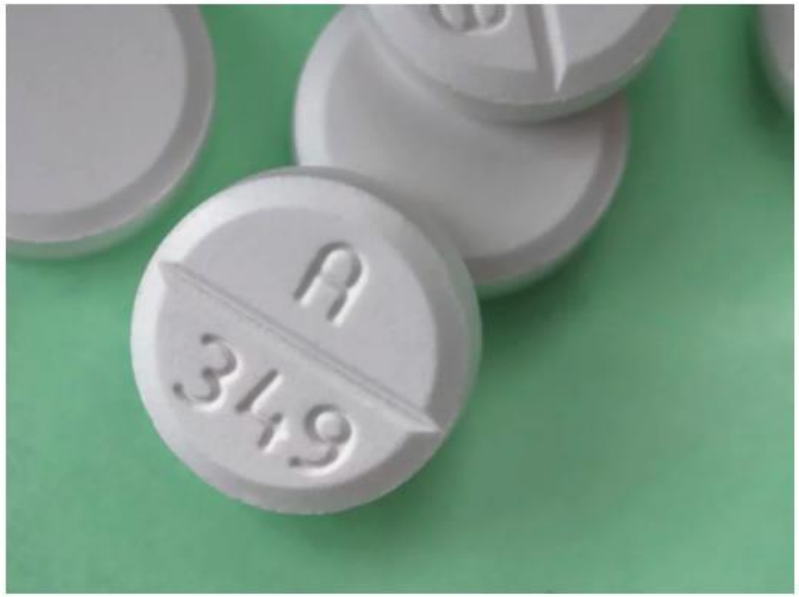
BUSINESS

3 of America's biggest pharmacy chains have been found liable for the opioid crisis

Updated November 23, 2021 · 8:23 PM ET
Heard on Morning Edition

BRIAN MANN

3-Minute Listen + PLAYLIST



Oxycodone pills. A federal jury in Ohio on Tuesday found major pharmacy chains liable for helping to fuel the opioid crisis.
Marie Hickman/Getty Images

A federal jury on Tuesday found three of the nation's biggest pharmacy chains, CVS, Walgreens and Walmart, liable for helping to fuel the U.S. opioid crisis — a decision that's expected to have legal repercussions as thousands of similar lawsuits move forward in courts across the country.

CNBC MARKETS

Purdue has
federal inves
violates ban
hand of othe
bankruptcy

1, 2020

pharma.html

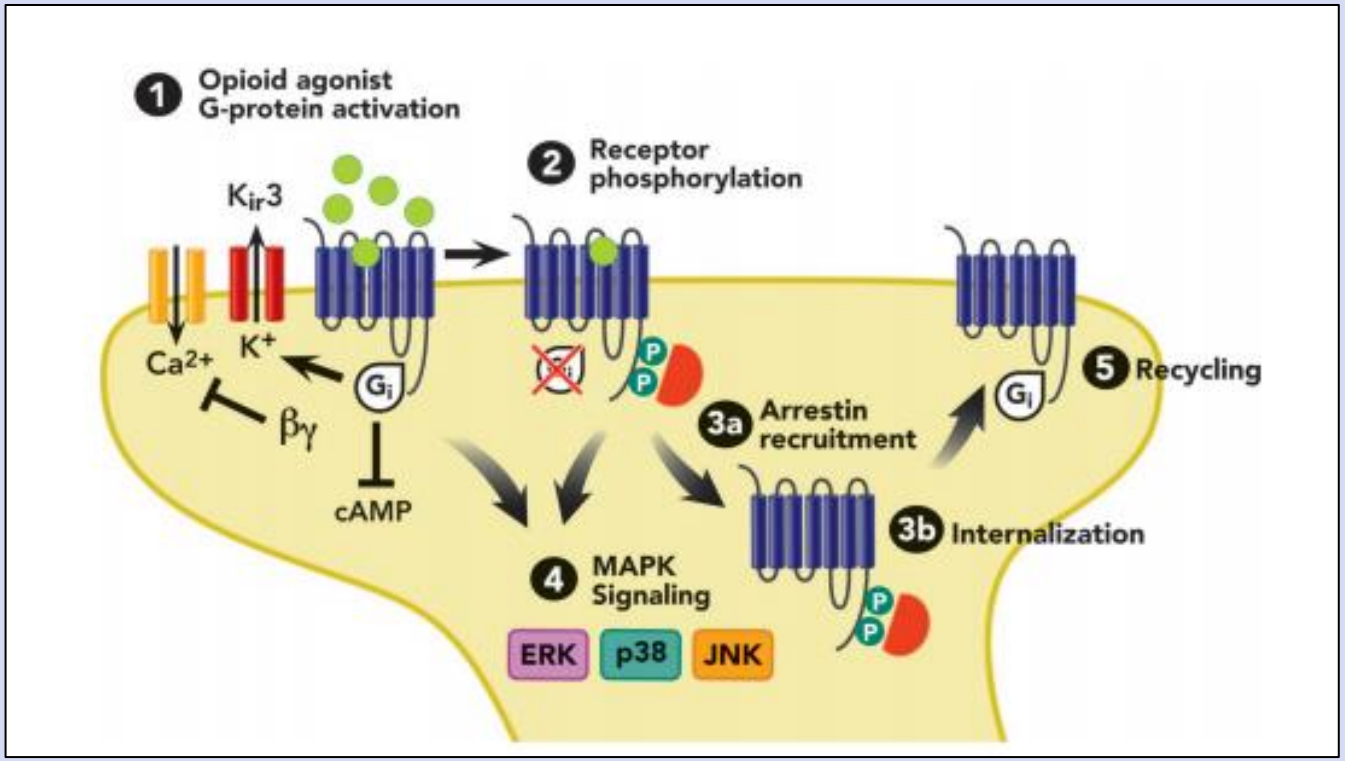
Opioids: Effects & Side Effects

Definition: opiate, opioid, narcotic

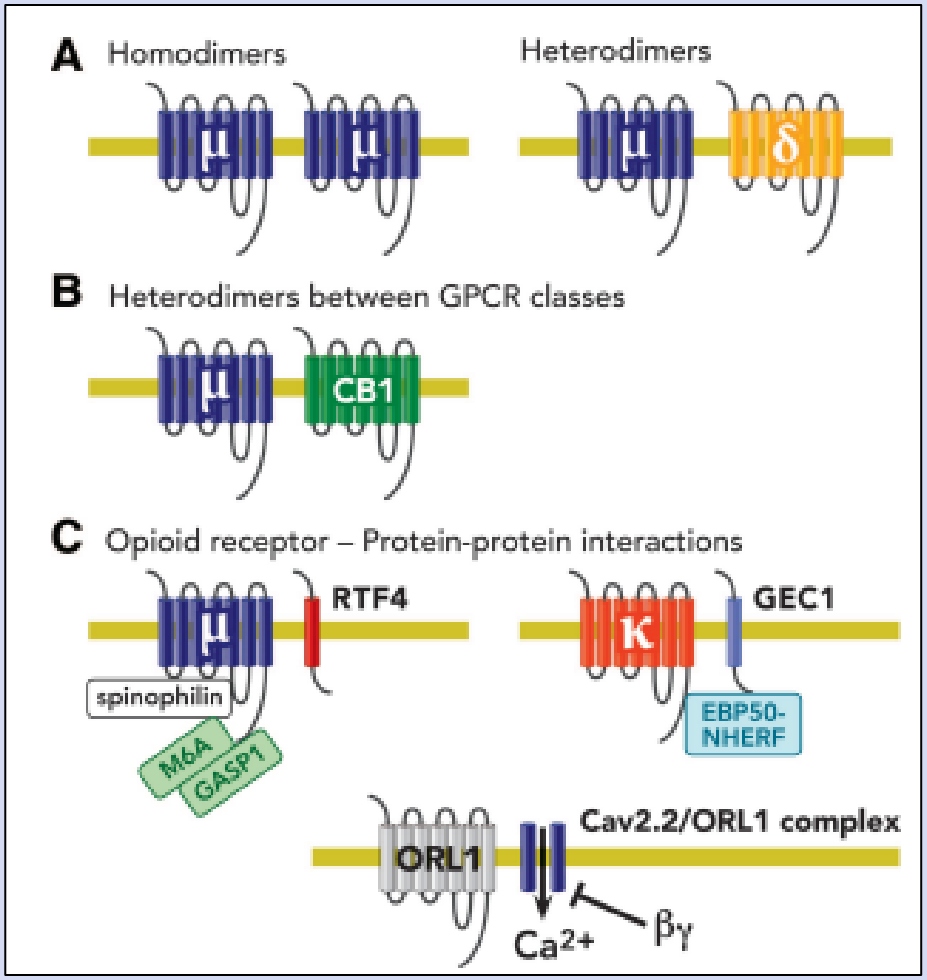
- Opiate: Drugs derived from the poppy *Papaver* somniferum.
- Opioid: Substances with activity on opioid receptors whether natural, synthetic or endogenous.
- Narcotic: A drug that causes insensibility or stupor.

Opioid receptors (mu, delta, kappa, ORL-1)

G-protein coupled



Al-Hasani. Anesthesiology 2011



Al-Hasani. Anesthesiology 2011

Opioid Effects - CNS

- **Analgesia (spinal & brain)**
- **Mood alteration including euphoria/reward**
- **Sedation, loss of consciousness**
- **Respiratory depression**
- **Nausea, vomiting**
- Truncal rigidity
- Decreased cough reflex
- Miosis
- Hyperalgesia (in humans?)

Opioid Effects - peripheral

Gastrointestinal

- Decreased motility & constipation
- Increased tone biliary system

Cardiovascular

- Bradycardia & hypotension

Neuroendocrine

- Decreased release of stress hormones
- Decreased release of hypothalamic hormones (irregular menses and decreased testosterone)

Other

- Immune: altered/impaired function - leukocytes have MOR’s
- Urinary retention
- Motor: myoclonus
- Skin: pruritis & sweating

Psychological Effects of Opioids - Taxonomy

Dependence:

- Drug causes a withdrawal syndrome upon cessation (occurs with addictive and non-addictive drugs).

Tolerance:

- A fixed dose causes a decreasing effect with repeated exposure.

Addiction:

- Compulsive use resulting in physical, psychological, and/or social dysfunction, and continued use despite dysfunction.

Long-term Opioid Therapy for Chronic Pain: Efficacy Data

Chronic Opioid Therapy - Efficacy

Review of electronic data bases including Medline/PubMed:

Search terms:

Opioids/opiates/narcotics/non-terminal pain/chronic non-malignant pain/chronic pain and combinations/clinical trial/review/meta-analysis/Cochrane review.

PubMed:

- No filter: thousands of citations
- Clinical trial: hundreds of citations

Long-term Opioid Therapy Efficacy Chronic Non-Cancer Pain

Long-term opioid management for chronic noncancer pain (Review)

Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, Schoelles KM

THE COCHRANE COLLABORATION®

Cochrane 2010:
Long-term opioid management for chronic non-cancer pain

Included studies:

- collected data for at least 6 months
- were full-text articles
- did not include redundant data
- were prospective; only one was a RCT’s (but no placebo)
- enrolled at least 10 participants

Cochrane 2010:
Long-term opioid management for chronic non-cancer pain

Results:
26 studies enrolling total of 4893 participants reviewed.

25 of the studies were case series or uncontrolled long-term trial continuations, the other was an RCT comparing two opioids.

Cochrane 2010:
Long-term opioid management for chronic non-cancer pain

Conclusions:

Many patients discontinue long-term opioid therapy due to adverse events or insufficient pain relief; however, weak evidence suggests that patients who are able to continue opioids long-term experience clinically significant pain relief.

Whether quality of life or functioning improves is inconclusive.

Many minor adverse events (like nausea and headache) occurred, but serious adverse events, including iatrogenic opioid addiction, were rare.

Long-term Opioid Therapy Efficacy Chronic Low Back Pain

Cochrane Collaboration 2014: Opioids and Chronic Low Back Pain

Spine

SPINE Volume 39, Number 7, pp 556-563

COCHRANE COLLABORATION

Opioi
Treatr

An Up

Conclusion. There is evidence of short-term efficacy (moderate for pain and small for function) of opioids to treat CLBP compared with placebo. The effectiveness and safety of long-term opioid therapy for treatment of CLBP remains unproven.

Key words: analgesics, opioid/adverse effects, opioid/

Luis Enrique Chaparro, MD,* Andrea D. Furlan, MD, PhD,† Amol Deshpande, MD,‡ Angela Mailis-Gagnon, MD, MSc, FRCPC,§ Steven Atlas, MD,¶ and Dennis C. Turk, PhD‖

Opioids for Chronic Low Back Pain: Chaparro et al, Cochrane 2014

- 15 randomized double blinded trials (5540 patients)
- Compared opioids and placebo or other treatments
- Outcomes included pain and function

Opioids for Chronic Low Back Pain:Chaparro et al, Cochrane 2014

- Tramadol was better than placebo for pain and function.
- Compared with placebo, transdermal buprenorphine decreased pain but did not improve function.
- Strong opioids were better than placebo for pain and function.
- Two trials found no difference between opioids and antidepressants for pain or function.

Opioids for Chronic Low Back Pain: Chaparro et al, Cochrane 2014

No serious adverse effects, risks (addiction or overdose), or complications were reported.

However: reviewed trials had low to moderate quality, high drop-out rates, short duration, and limited interpretability of functional improvement.

Only two of the trials were longer than 3 months, the longest was only 15 weeks.

Long-term Opioid Therapy Efficacy Neuropathic Pain

5 randomized, double-blind cross-over studies of 5-7 weeks (n=236)

AUTHORS' CONCLUSIONS: "There was insufficient evidence to support or refute the suggestion that morphine has any efficacy in any neuropathic pain condition."

JAMA | Original Investigation

2018

Opioids for Chronic Noncancer Pain

A Systematic Review and Meta-analysis

Jason W. Busse, DC, PhD; Li Wang, PhD; Mostafa Kamaleldin, MB BCh; Samantha Craigie, MSc; John J. Riva, DC, MSc; Luis Montoya, DDS, MSc; Sohail M. Mulla, PhD; Luciane C. Lopes, ScD, MSc; Nicole Vogel, PhD; Eric Chen, BHSc; Karin Kirmayr, MD; Kyle De Oliveira, MD; Lori Olivieri, MD; Alka Kaushal, MBBS, DA; Luis E. Chaparro, MD; Inna Oyberman, MD; Arnav Agarwal, MD; Rachel Couban, MA, MISt; Ludwig Tsoi, MBChB; Tommy Lam, MBBS; Per Olav Vandvik, MD, PhD; Sandy Hsu, BA; Malgorzata M. Bala, MD; Stefan Schandelmaier, MD; Anne Scheidecker, MD; Shanil Ebrahim, PhD; Vahid Ashoorion, MD, PhD; Yasir Rehman, MD, MSc; Patrick J. Hong, BMSc; Stephanie Ross, PhD; Bradley C. Johnston, PhD; Regina Kunz, MD, MSc; Xin Sun, PhD; Norman Buckley, MD; Daniel I. Sessler, MD; Gordon H. Guyatt, MD, MSc

- Meta-analysis of 96 RCTs including 26,169 subjects.
- Compared with placebo opioid use is associated with:
  - reduced pain
    - 0.69 on 10-point scale
  - improved function
    - 2 on 100-point scale
  - increased vomiting
- Low to moderate evidence suggests opioids are superior to NSAIDs, TCAs, and anticonvulsants.

JAMA | Original Investigation

JAMA. 2018;320(23).

Opioids for Chronic Noncancer Pain
A Systematic Review and Meta-analysis

Jason W. Busse, DC, PhD; Li Wang, PhD; Mostafa Kamaleldin, MB BCh; Samantha Craigie, MSc; John J. Riva, DC, MSc; Luis Montoya, DDS, MSc; Sohail M. Mulla, PhD; Luciane C. Lopes, ScD, MSc; Nicole Vogel, PhD; Eric Chen, BHSc; Karin Kirmayr, MD; Kyle De Oliveira, MD; Lori Olivieri, MD; Alka Kaushal, MBBS, DA; Luis E. Chaparro, MD; Inna Oyberman, MD; Arnav Agarwal, MD; Rachel Couban, MA, MISt; Ludwig Tsoi, MBChB; Tommy Lam, MBBS; Per Olav Vandvik, MD, PhD; Sandy Hsu, BA; Malgorzata M. Bala, MD; Stefan Schandelmaier, MD; Anne Scheidecker, MD; Shanil Ebrahim, PhD; Vahid Ashoorion, MD, PhD; Yasir Rehman, MD, MSc; Patrick J. Hong, BMSc; Stephanie Ross, PhD; Bradley C. Johnston, PhD;

CONCLUSIONS AND RELEVANCE In this meta-analysis of RCTs of patients with chronic noncancer pain, evidence from high-quality studies showed that opioid use was associated with statistically significant but small improvements in pain and physical functioning, and increased risk of vomiting compared with placebo. Comparisons of opioids with nonopioid alternatives suggested that the benefit for pain and functioning may be similar, although the evidence was from studies of only low to moderate quality.

JAMA | Original Investigation

Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain
The SPACE Randomized Clinical Trial

Erin E. Krebs, MD, MPH; Amy Gravely, MA; Sean Nugent, BA; Agnes C. Jensen, MPH; Beth DeRonne, PharmD; Elizabeth S. Goldsmith, MD, MS; Kurt Kroenke, MD; Matthew J. Bair; Siamak Noorbaloochi, PhD

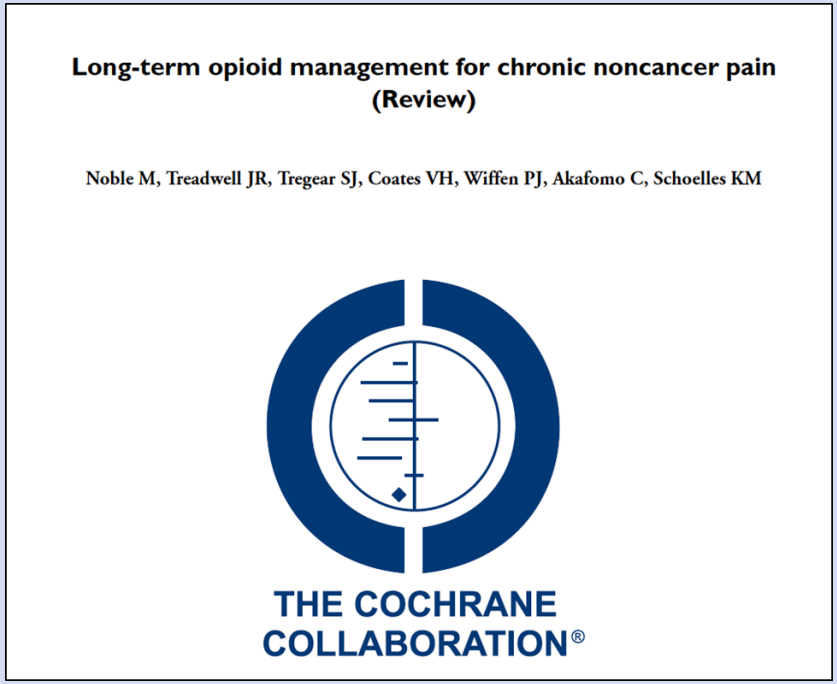
JAMA. 2018;319(9).

CONCLUSIONS AND RELEVANCE Treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function over 12 months. Results do not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain.

Long-term Opioid Therapy Efficacy
Iatrogenic Addiction

Cochrane 2010:
Long-term opioid management for chronic non-cancer pain

- Iatrogenic addiction is approx 0.3% in patients <u>without</u> major risk factors



Opioids for post-operative pain: risk of long-term use

Rates and risk factors for prolonged opioid use after major surgery: population based cohort study

OPEN ACCESS

Hance Clarke *assistant professor*[1 2 3], Neilesh Soneji *lecturer*[2 4], Dennis T Ko *associate professor*[5 6 7], Lingsong Yun *analyst*[4], Duminda N Wijeysundera *assistant professor*[1 2 5 7 8]

[1]Department of Anesthesia and Pain Management, Toronto General Hospital, 200 Elizabeth Street, Eaton North 3 EB 317, Toronto, ON, Canada, M5G 2C4; [2]Department of Anesthesia, University of Toronto, Canada; [3]Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, Canada; [4]Department of Anesthesia and Pain Management, Toronto Western Hospital, Canada; [5]Institute for Clinical Evaluative Sciences, Toronto, Canada; [6]Division of Cardiology, Schulich Heart Centre, Sunnybrook Health Sciences Centre, University of Toronto, Canada; [7]Institute of Health Policy Management and Evaluation, University of Toronto, Canada; [8]Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, Ontario, Canada

BMJ 2014

- Only 3% of previously opioid naive patients still taking opioids at 90 days after major elective surgery

Risk Factors for Prolonged Opioid Use Following Spine Surgery, and the Association with Surgical Intensity, Among Opioid-Naive Patients

Andrew J. Schoenfeld, MD, MSc, Kenneth Nwosu, MD, Wei Jiang, MS, Allan L. Yau, BS, Muhammad Ali Chaudhary, MD, Rebecca E. Scully, MD, Tracey Koehlmoos, PhD, MHA, James D. Kang, MD, and Adil H. Haider, MD, MPH

Investigation performed at the Center for Surgery and Public Health, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts

J Bone Joint Surg 2017

- Virtually all patients are off opioids by 6 months post-op
  (this was a low-risk population given the exclusion criteria)

Opioid Induced Hyperalgesia

"There is not sufficient evidence to support or refute the existence of OIH in humans except in the case of normal volunteers receiving opioid infusions."

Do Opioids Induce Hyperalgesia in Humans? An Evidence-Based Structured Review, Fishbain et al (2008)

"Findings of the clinical prevalence of OIH are not available."

A Comprehensive Review of Opioid-Induced Hyperalgesia, Lee et al (2011)

Efficacy of Opioids for Chronic Pain: Summary

- Evidence regarding the efficacy of “long-term” opioid therapy for chronic pain is extremely limited and high-quality data essentially non-existent.
- Evidence regarding side effects from long-term opioid therapy for chronic pain is also very limited but would indicate opioids are well-tolerated by most individuals.

Risk Mitigation:
State and Federal Efforts

Opioid Therapy: Federal and State Efforts

Recognition of the major individual and societal problems associated with prescription opioids has led to a variety of initiatives:

- Administrative-regulatory changes (including multi-state PMP's)
- Provider education (including REMS)
- Patient education
- Increased DoJ and DEA administrative and criminal actions

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 65
March 15, 2016

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

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

Determining When to Initiate or Continue Opioids for Chronic Pain

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

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

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

Assessing Risk and Addressing Harms of Opioid Use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

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

April 9, 2019 CDC issued a clarification letter:

- Stressed that the guidelines weren't intended for patients with cancer, sickle cell disease, or post-op pain.
- Stated that the guidelines weren't designed to "deny any patients who suffer with chronic pain" the option of opioid medications.
- Stated that patients should not be denied coverage for their opioid medications.

April 10, 2019 CDC director Robert Redfield:

Acknowledged that the 2016 CDC guideline was causing patient harm -

- “CDC is working diligently to evaluate the impact of the Guideline and clarify its recommendations to help reduce unintended harms”
- “The Guideline includes recommendations for clinicians to work with patients to taper or reduce dosage *only* when patient harm outweighs patient benefit of opioid therapy.”

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

JUNE 13, 2019

No Shortcuts to Safer Opioid Prescribing

Deborah Dowell, M.D., M.P.H., Tamara Haegerich, Ph.D., and Roger Chou, M.D.

Since the Centers for Disease Control and Prevention (CDC) released its Guideline for Prescribing Opioids for Chronic Pain in 2016,[1] the medical and health policy communities have largely embraced

ommended dosage and duration thresholds and policies that encourage hard limits and abrupt tapering of drug dosages, resulting in sudden opioid discontinuation or dismissal of patients

Dowell et al, 2019

- "Unfortunately, **some policies and practices purportedly derived from the guideline have been inconsistent with its recommendations**."
- "…inconsistencies which include inflexible application of recommended dosage and duration thresholds and policies that encourage hard limits and abrupt tapering of drug dosages, **resulting in sudden opioid discontinuation or dismissal of patients from a physician's practice**."
- The guideline "**does not address or suggest discontinuation of opioids already prescribed at higher dosages**." (so called 'legacy patients')

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering

Safety Announcement

[4-9-2019] The U.S. Food and Drug Administration (FDA) has received reports of serious harm in patients who are physically dependent on opioid pain medicines suddenly having these medicines discontinued or the dose rapidly decreased. These include

Rapid discontinuation can result in uncontrolled pain or withdrawal symptoms. In turn, these symptoms can lead patients to seek other sources of opioid pain medicines, which may be confused with drug-seeking for abuse. Patients may attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

decrease the dose in patients who are physically dependent on opioid pain medicines when the dose is to be decreased or the medicine is to be discontinued.

Rapid discontinuation can result in uncontrolled pain or withdrawal symptoms. In turn, these symptoms can lead patients to seek other sources of opioid pain medicines, which may be confused with drug-seeking for abuse. Patients may attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

CDC Released Draft Revised Guidelines

- Released Feb 2022; comment period ended April 11; expected release end 2022.
- Removed opioid dosage limits/cautions (statement 5).
- Removed limit on duration of opioid therapy for acute pain (statement 6).
- Changed recommended PDMP check from every Rx to every 3 months when starting opioids and periodically thereafter (statement 9)
- Changed recommended U-tox form when starting opioids and annually to “consider toxicology testing” (statement 10)
- Changed caution re concurrent Rx of opioids and benzodiazepines from “avoid…whenever possible” to “use extreme caution” (statement 11)

Long-term Therapy for Chronic Pain: Summary & Recommendations

Chronic Opioid Therapy: General Principles

- Don’t rush to initiate opioid therapy, particularly if you have not cared for the patient longitudinally. Employ a step-wise approach to pain treatment; opioids are not typically the first step.
- Prior to initiating opioids:
  - Clearly discuss goals of therapy with indicators of success and ‘failure’
  - Opioid agreement (communication tool)
  - Toxicology at time of initial request
  - Psychological assessment to identify major risk factors
- Start low, go slow, and don’t titrate to heroic doses
- Regular, meaningful reassessment; discontinue when appropriate.
- Use abuse-deterrent formulations whenever possible.

Chronic Opioid Therapy: General Principles

Trust but verify

- Call other providers (**communication** is key)
- Check prescription monitoring program with every Rx
- Random toxicology (urine)
  - Provide a little rope when appropriate.
  - Frequency is patient-dependent.
  - Discuss apparently aberrant results with a clinical pathologist.
  - Gas chromatography–mass spectrometry as appropriate

Opioid Therapy – other thoughts…

- Remain open minded; there is much more that we don't know than we do know.

- Don't be an extremist.
  - I never prescribe (OIH)
  - 60-90 MME is an appropriate max dose for all patients.

- Identification of at-risk individuals is essential.

Refuse to Provide or Stop Opioid Therapy

Major red flag behaviors

- Diversion
- Violence, theft and other criminal behaviors

- High risk individuals?
- One or two episodes of ‘yellow flag’ behaviors?

Knowledge Gaps & Unmet Needs

- Improved caregiver & patient education.
- Better abuse deterrent technologies.
- MOR agonists with better analgesia / adverse effect profile ?

The Future – Better MOR Agonists?

J Pain Res. 2021; 14: 969–979.
Published online 2021 Apr 14. doi: 10.2147/JPR.S278279
PMCID: PMC8054572
PMID: 33889018

Oliceridine: A Novel Drug for the Management of Moderate to Severe Acute Pain – A Review of Current Evidence

Hon Sen Tan[1] and Ashraf S Habib[2]

Abstract

Go to:

Optimal pain relief requires a balance between adequate analgesia and risk of adverse effects. Opioids remain the cornerstone for managing moderate to severe pain, but are associated with opioid-induced respiratory depression (OIRD) and gastrointestinal complications. Opioids exert their analgesic effects predominantly via G-protein signaling, however, adverse effects including OIRD are mediated by the β-arrestin pathway. Oliceridine is the first of a new class of biased opioid agonists that preferentially activate G-protein signaling over β-arrestin, which would theoretically improve analgesia and reduce the risk of adverse effects. Oliceridine is approved by the Food and Drug Administration (FDA) for the treatment of

ARTICLE

Stru
anal

Aashish Mar
Ralf C. Kling
Da Duan[2], G

Levit[2],
Löber[4],

Morphine i
opioids—w
through th
confer ana
scaffolds u
selectivity
component of analgesia versus the reflexive component and is devoid of both respiratory depression and morphine-like reinforcing activity in mice at equi-analgesic doses. PZM21 thus serves as both a probe to disentangle μOR signalling and a therapeutic lead that is devoid of many of the side effects of current opioids.

and related
) signalling
thought to
lentify new
exceptional
he affective

8/nature19112

8 April 2022

NEWS IN BRIEF | 08 April 2022

Vertex's $Na_V1.8$ inhibitor passes phase II pain point

Asher Mullard

Vertex's $Na_V1.8$-targeted VX-548 reduced acute pain in two phase II trials — following abdominoplasty or bunionectomy surgery — paving the way for a pivotal trial of the non-opioid pain reliever.

The Na_V sodium channels are a family of transmembrane ion channels with key roles in various aspects of biology. $Na_V1.7$ first attracted attention as a possible analgesic target nearly 20 years ago, following reports that gain-of-function mutations can cause erythromelalgia and pain hypersensitivity in humans, and loss-of-function mutations can abrogate pain perception.

Multiple $Na_V1.7$ inhibitors have stalled in the clinic, due to lack of efficacy. The related $Na_V1.8$ sodium channel offers similar analgesic opportunity, but has also proven challenging to target: VX-548 is Vertex's fourth $Na_V1.8$ inhibitor to make it into the clinic. In two proof-of-concept phase II trials, a high dose — but not the mid and low doses — of VX-548 met the primary endpoint, improvement in the Sum of Pain Intensity Difference over 48 hours.

Vertex plans to advance the drug into pivotal trials in the second half of 2022.

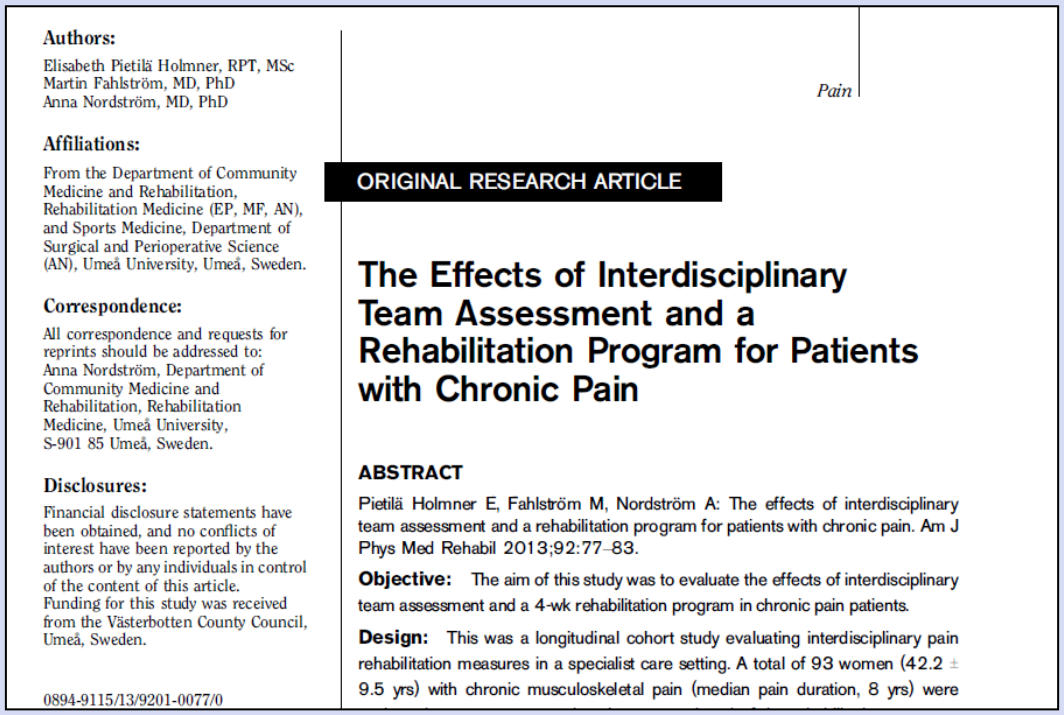
Various other novel analgesics are also in development.

Nature Reviews Drug Discovery **21**, 327 (2022)

doi: https://doi-org.ezp-prod1.hul.harvard.edu/10.1038/d41573-022-00070-w

Long-term Therapy for Chronic Pain
Final Thoughts

Chronic Opioid Therapy is Rarely a Monotherapy



Authors:

Elisabeth Pietilä Holmner, RPT, MSc
Martin Fahlström, MD, PhD
Anna Nordström, MD, PhD

Affiliations:

From the Department of Community Medicine and Rehabilitation, Rehabilitation Medicine (EP, MF, AN), and Sports Medicine, Department of Surgical and Perioperative Science (AN), Umeå University, Umeå, Sweden.

Correspondence:

All correspondence and requests for reprints should be addressed to: Anna Nordström, Department of Community Medicine and Rehabilitation, Rehabilitation Medicine, Umeå University, S-901 85 Umeå, Sweden.

Disclosures:

Financial disclosure statements have been obtained, and no conflicts of interest have been reported by the authors or by any individuals in control of the content of this article.
Funding for this study was received from the Västerbotten County Council, Umeå, Sweden.

0894-9115/13/9201-0077/0

ORIGINAL RESEARCH ARTICLE

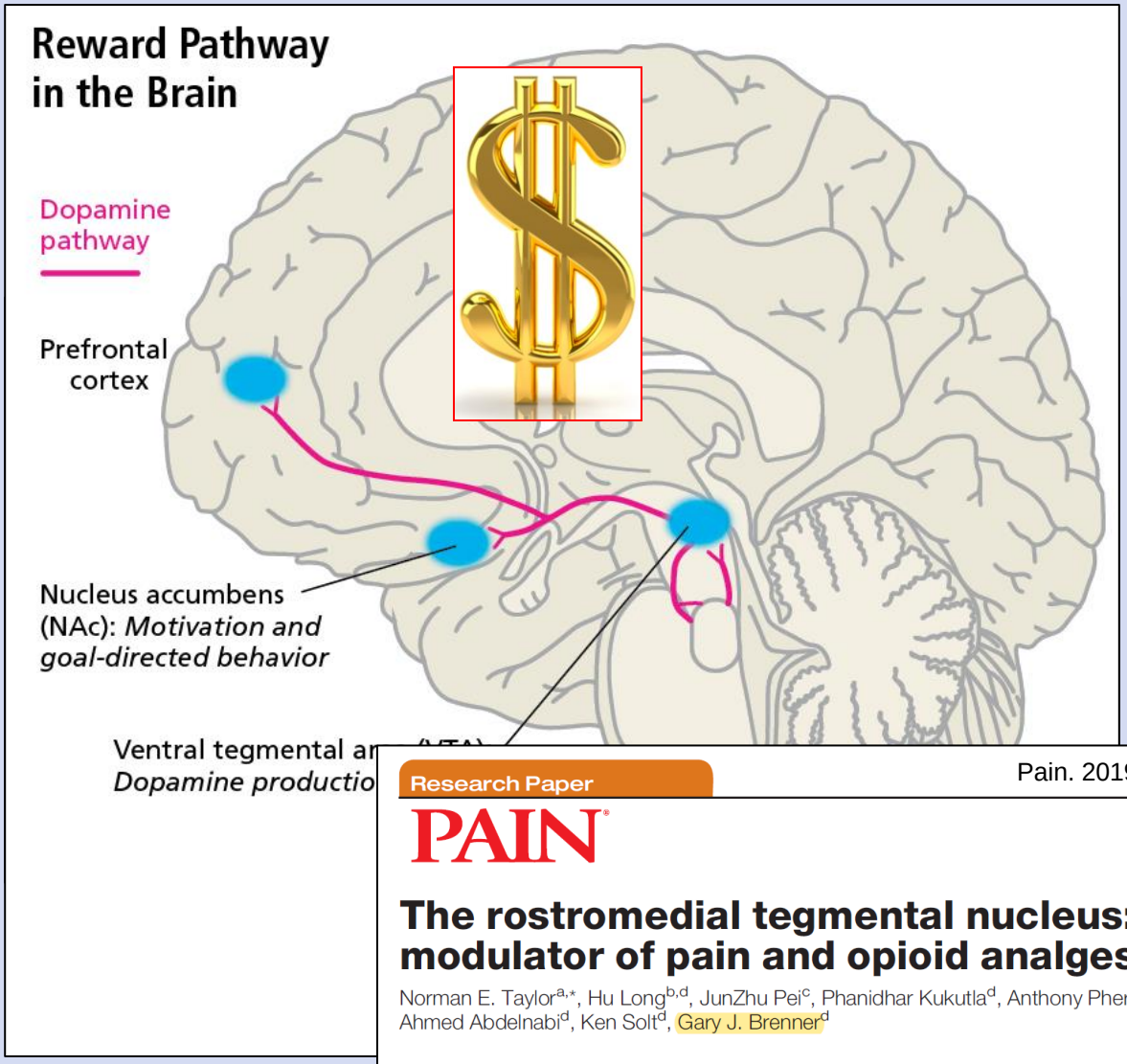
The Effects of Interdisciplinary Team Assessment and a Rehabilitation Program for Patients with Chronic Pain

ABSTRACT

Pietilä Holmner E, Fahlström M, Nordström A: The effects of interdisciplinary team assessment and a rehabilitation program for patients with chronic pain. Am J Phys Med Rehabil 2013;92:77–83.

Objective: The aim of this study was to evaluate the effects of interdisciplinary team assessment and a 4-wk rehabilitation program in chronic pain patients.

Design: This was a longitudinal cohort study evaluating interdisciplinary pain rehabilitation measures in a specialist care setting. A total of 93 women (42.2 ± 9.5 yrs) with chronic musculoskeletal pain (median pain duration, 8 yrs) were

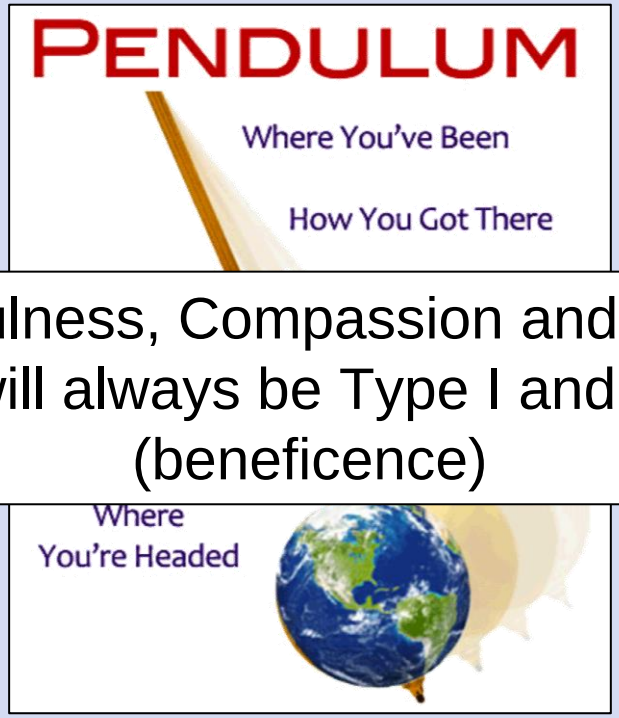


Research Paper
PAIN
Pain. 2019 Nov;160(11):2524-2534

The rostromedial tegmental nucleus: a key modulator of pain and opioid analgesia

Norman E. Taylor[a,*], Hu Long[b,d], JunZhu Pei[c], Phanidhar Kukutla[d], Anthony Phero[a], Farnaz Hadaegh[d], Ahmed Abdelnabi[d], Ken Solt[d], Gary J. Brenner[d]

Abstract
A recently defined structure, the rostromedial tegmental nucleus (RMTg; aka tail of the ventral tegmental area [VTA]), has been proposed as an inhibitory control center for dopaminergic activity of the VTA. This region is composed of GABAergic cells that send afferent projections to the ventral midbrain and synapse onto dopaminergic cells in the VTA and substantia nigra. These cells exhibit μ-opioid receptor immunoreactivity, and in vivo, ex vivo, and optogenetic/electrophysiological approaches demonstrate that morphine excites dopamine neurons by targeting receptors on GABAergic neurons localized in the RMTg. This suggests that the



Thoughtfulness, Compassion and Courage: there will always be Type I and II error (beneficence)

Thank You

2013 FSMB Policy Statement

Federation of STATE MEDICAL BOARDS

MODEL POLICY ON THE USE OF OPIOID ANALGESICS IN THE TREATMENT OF CHRONIC PAIN

Adopted as policy by the House of Delegates of the Federation of State Medical Boards in July 2013

INTRODUCTION

The Federation of State Medical Boards (FSMB) is committed to assisting state Medical Boards in protecting the public and improving the quality and integrity of health care in the United States. In 1997, the FSMB undertook an initiative to develop model guidelines and to encourage state medical boards and other health care regulatory agencies to adopt policies encouraging safe and effective treatment of patients with pain, including, if indicated, the use of opioid analgesics. [1]. The FSMB updated its guidelines in 2003 [2] so that its Model Policy would reflect the best available evidence on management of pain and give adequate attention to both the undertreatment and overtreatment of pain and the inappropriate use of opioid analgesics.

2013 FSMB Policy Statement: Departures from Best Clinical Practices

Inadequate attention to initial assessment to determine if opioids are clinically indicated and to determine risks associate with their use in a particular individual with pain.

Inadequate monitoring during the use of potentially abusable medications

- Dose reduction/weaning off should occur as indicated.

Inadequate attention to patient education and informed consent – this is a shared decision.

Unjustified dose escalation without adequate attention to risks or alternative treatments.

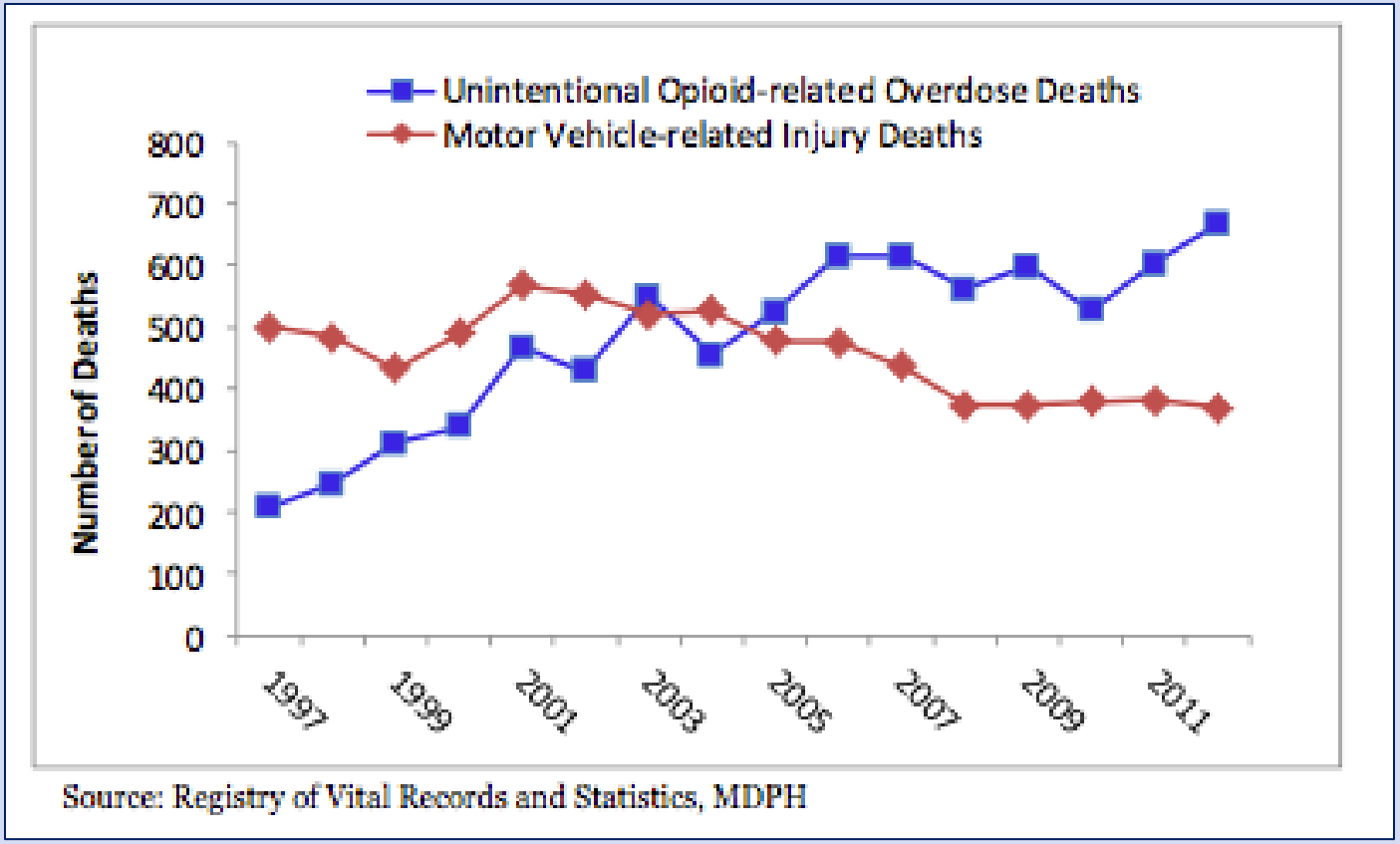
Excessive reliance on opioids, particularly high dose opioids for chronic pain management.

- Opioids for chronic pain only when other safer, potentially efficacious options have failed.
- Keep dose as low as possible.
- Continue opioids only if clear, objective outcomes are being met.

Not making use of available tools for risk mitigation.

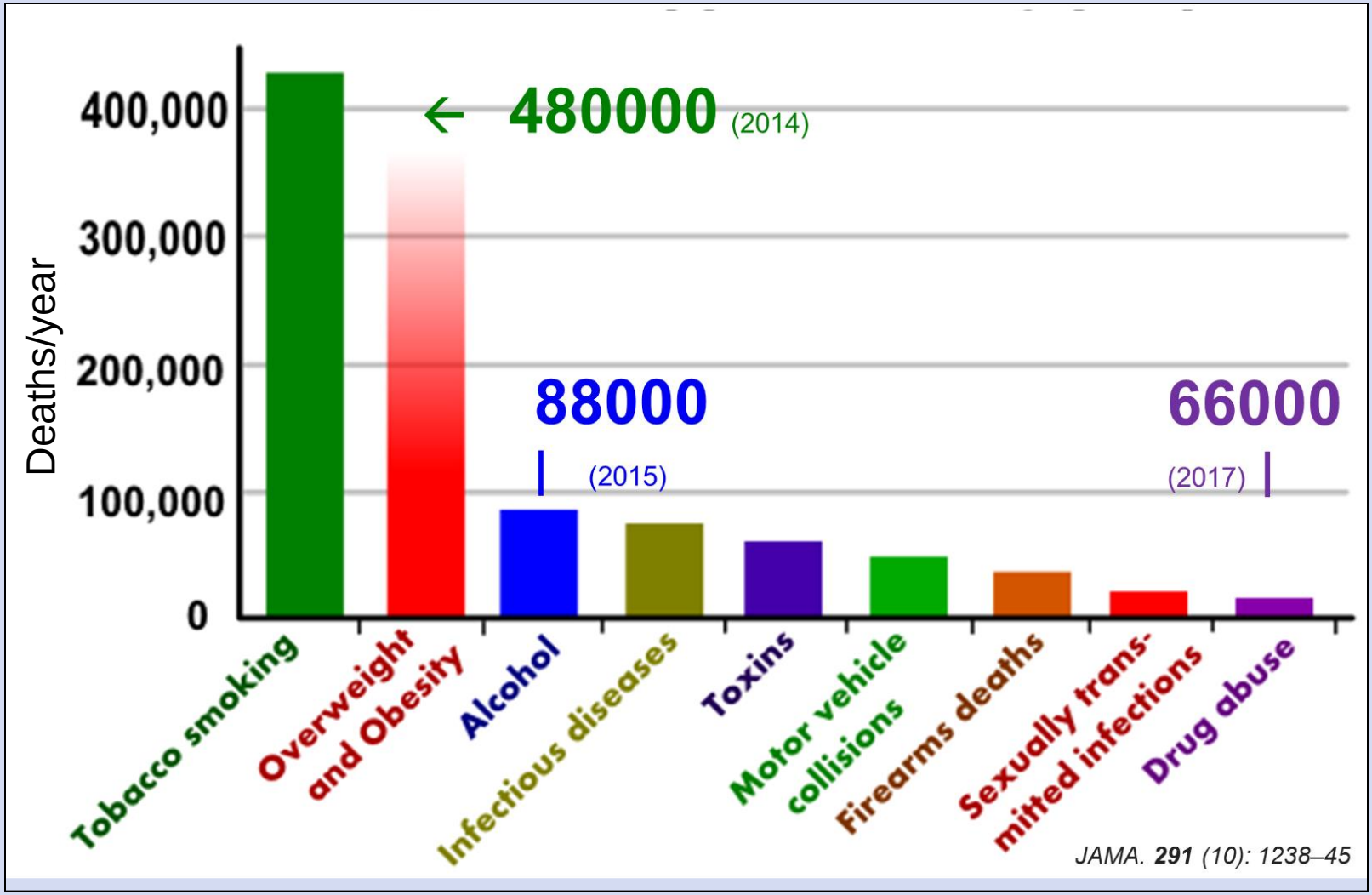
- PMP, random toxicology, ancillary care (e.g., psychology/psychiatry), etc.

Deaths in MA due to Opioid Overdose & MVA



Source: Registry of Vital Records and Statistics, MDPH

Preventable Causes of Death (U.S.)



Cochrane Collaboration 2013: Opioids and Neuropathic Pain

[Intervention Review]

Opioids for neuropathic pain

Authors' conclusions

Since the last version of this review, new studies were found providing additional information. Data were reanalyzed but the results did not alter any of our previously published conclusions. Short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain. Intermediate-term studies demonstrated significant efficacy of opioids over placebo, but these results are likely to be subject to significant bias because of small size, short duration, and potentially inadequate handling of dropouts. Analgesic efficacy of opioids in chronic neuropathic pain is subject to considerable uncertainty. Reported adverse events of opioids were common but not life-threatening. Further randomized controlled trials are needed to establish unbiased estimates of long-term efficacy, safety (including addiction potential), and effects on quality of life.

Review content assessed as up-to-date: 21 August 2013.

Citation: McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No.: CD006146. DOI: 10.1002/14651858.CD006146.pub2.

Cochrane Collaboration 2013: Opioids and Neuropathic Pain

- 39 studies (1237 subjects)
- Maximum trial length was 12 weeks

Conclusions:

- Analgesic efficacy of opioids in chronic neuropathic pain is subject to considerable uncertainty.
- Reported adverse events of opioids were common but not life-threatening.