

OPIOID-SPARING & ADVERSE EFFECTS OF OPIOIDS: ASSESSMENT AND ANALYSIS



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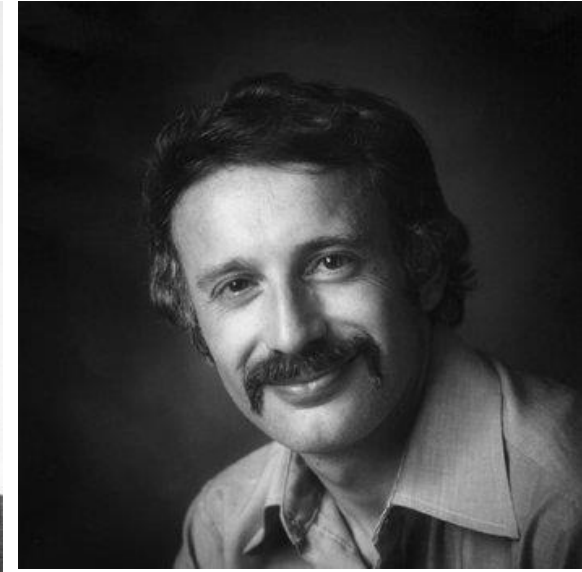
Opiate Receptors and Enkephalins



Solomon Snyder, Candace Pert
Johns Hopkins- 1973



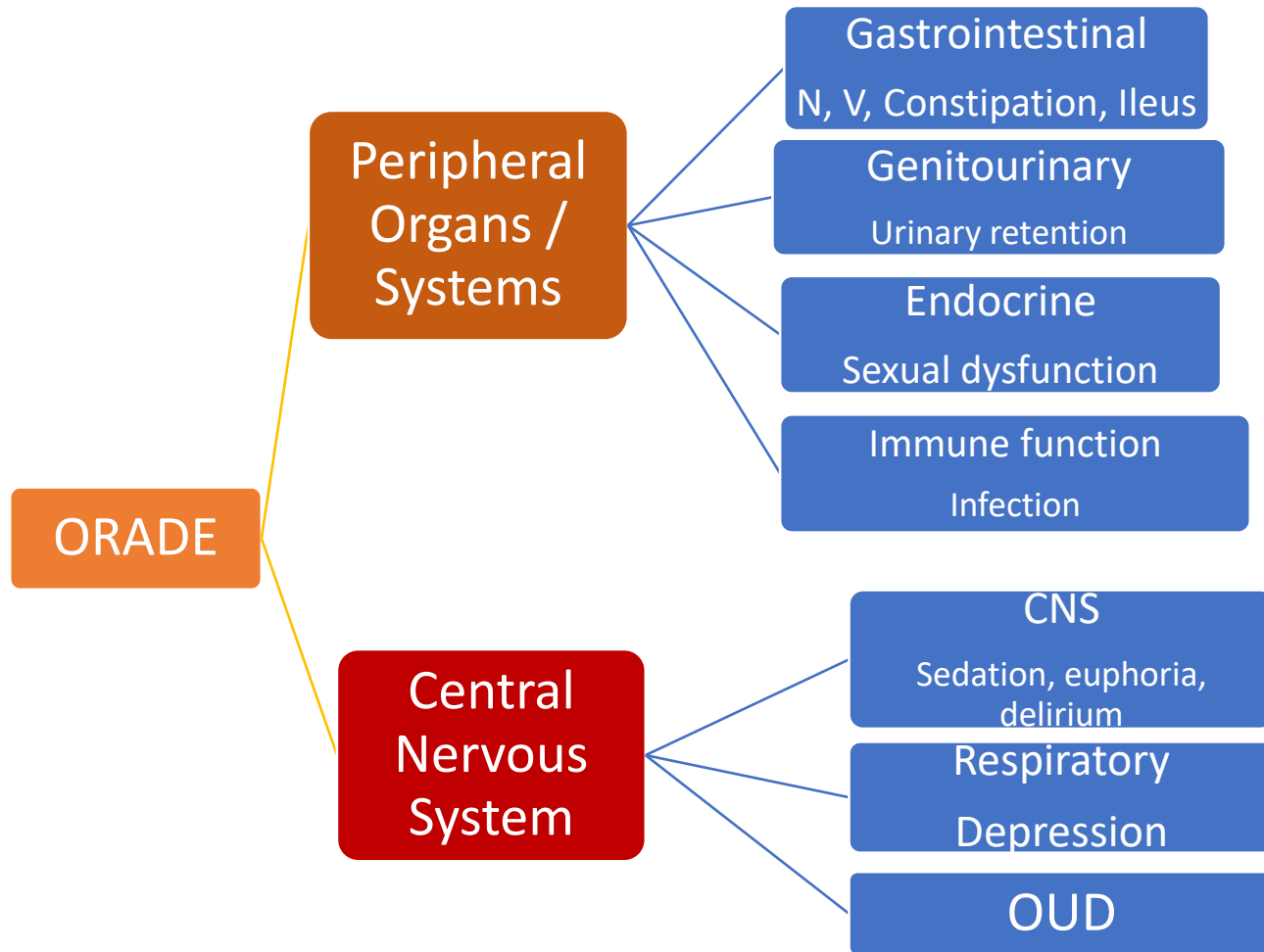
Hans W. Koserlitz
University of Aberdeen



John Hughes
Imperial College of
Science & Technology

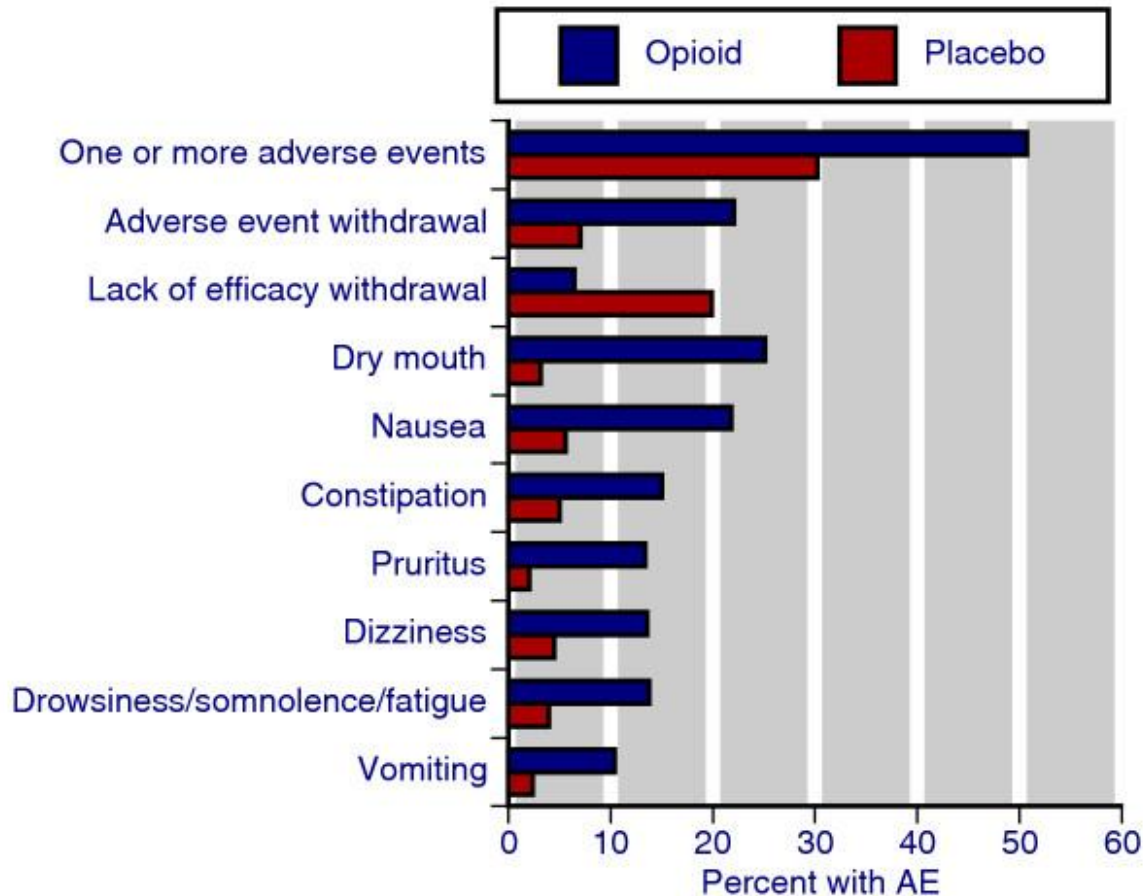
**1978 Albert Lasker Basic Medical
Research Award**

Opioids for Pain & Adverse Effects



ORADE: opioid-related adverse drug effects

Opioid adverse effects in chronic non-cancer pain RCTs

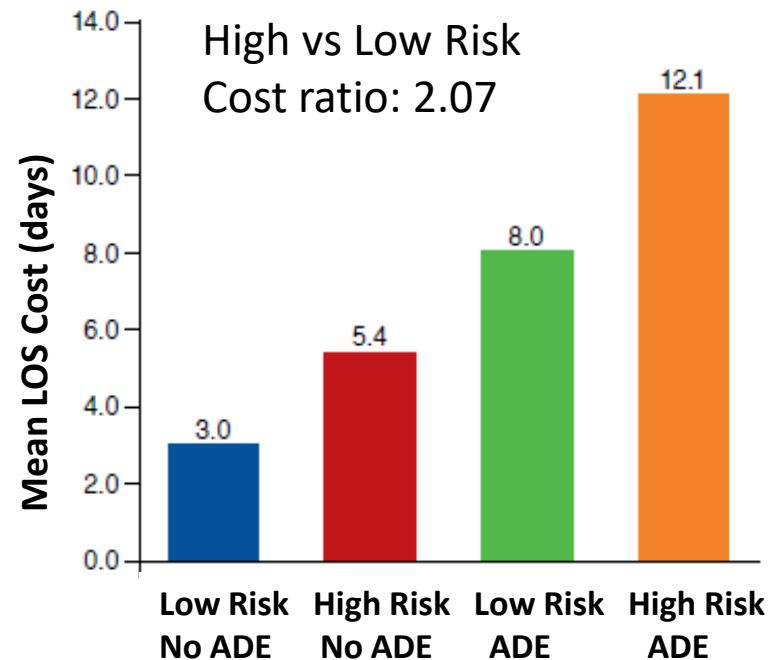
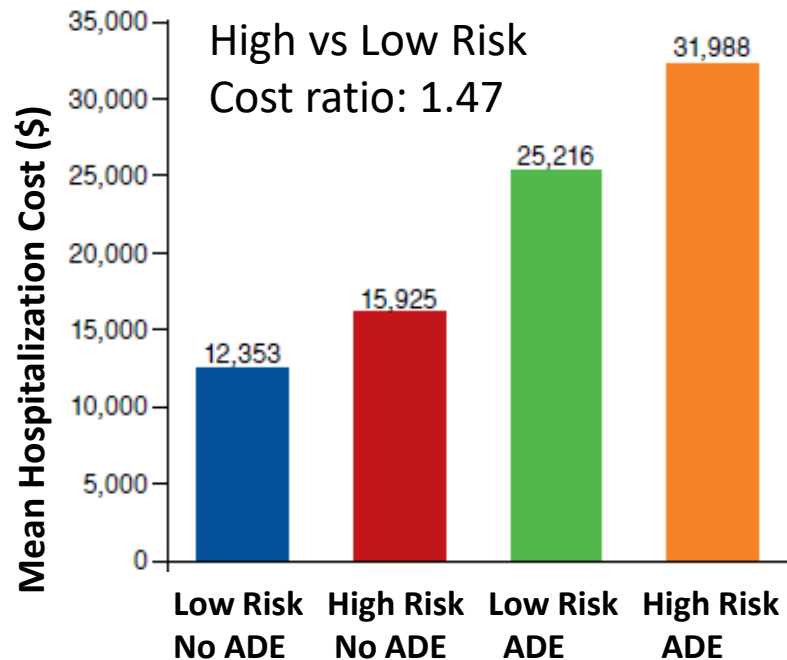


Risks: Incidence

- Resp. depression <1 %
- Falls/fractures 1-2%
- Constipation 30-40 %
- Hormonal effects 25-75%
- Sedation 15%
- Sleep disruption 25%
- Depression 30-40 %

Mean Hospitalization Cost and Length of Stay by Risk x ORADE Status

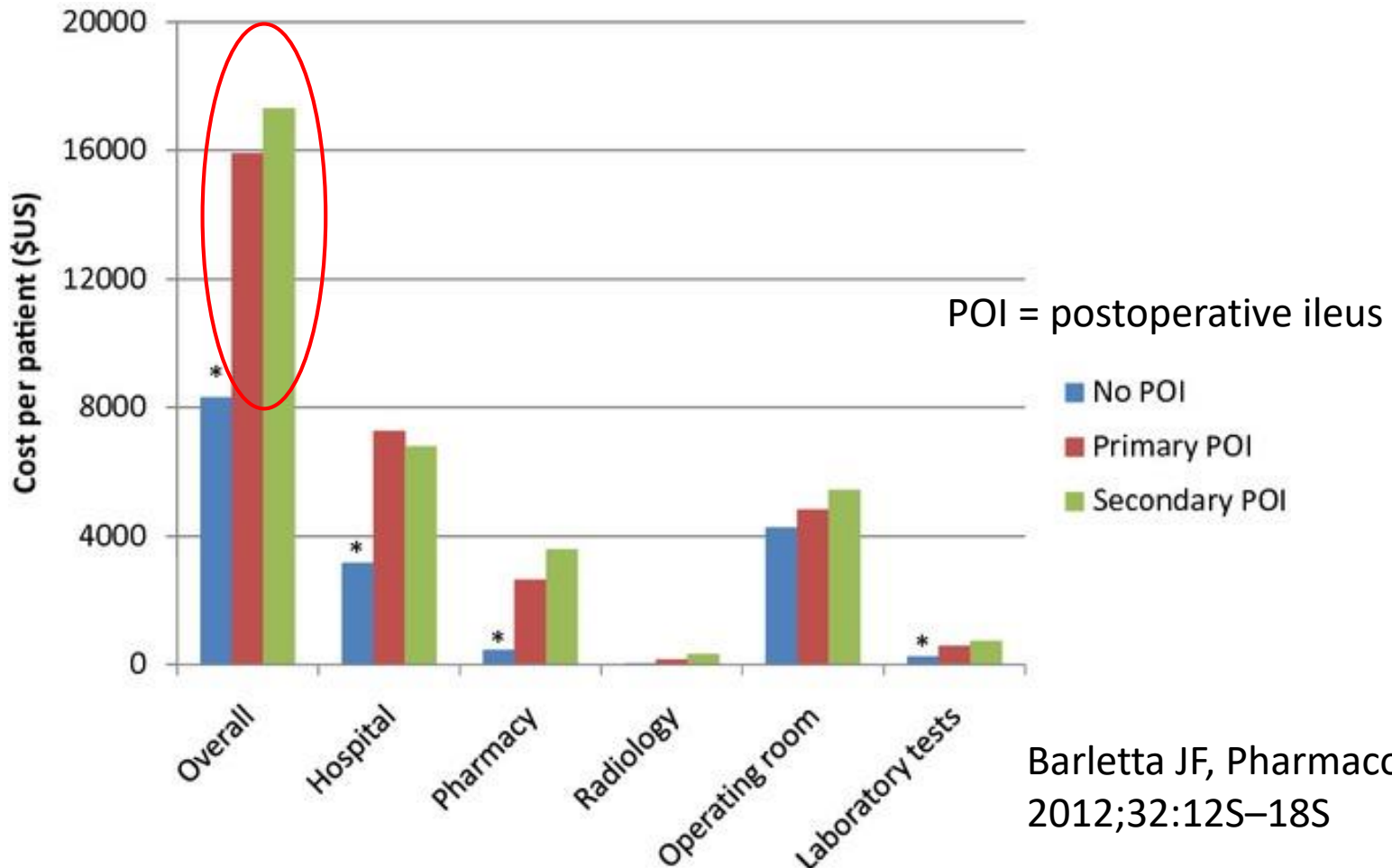
12 month G.I. surgical patients, N= 3,684



ADE = adverse drug event; LOS = length of stay;
ORADE = opioid-related adverse drug event.

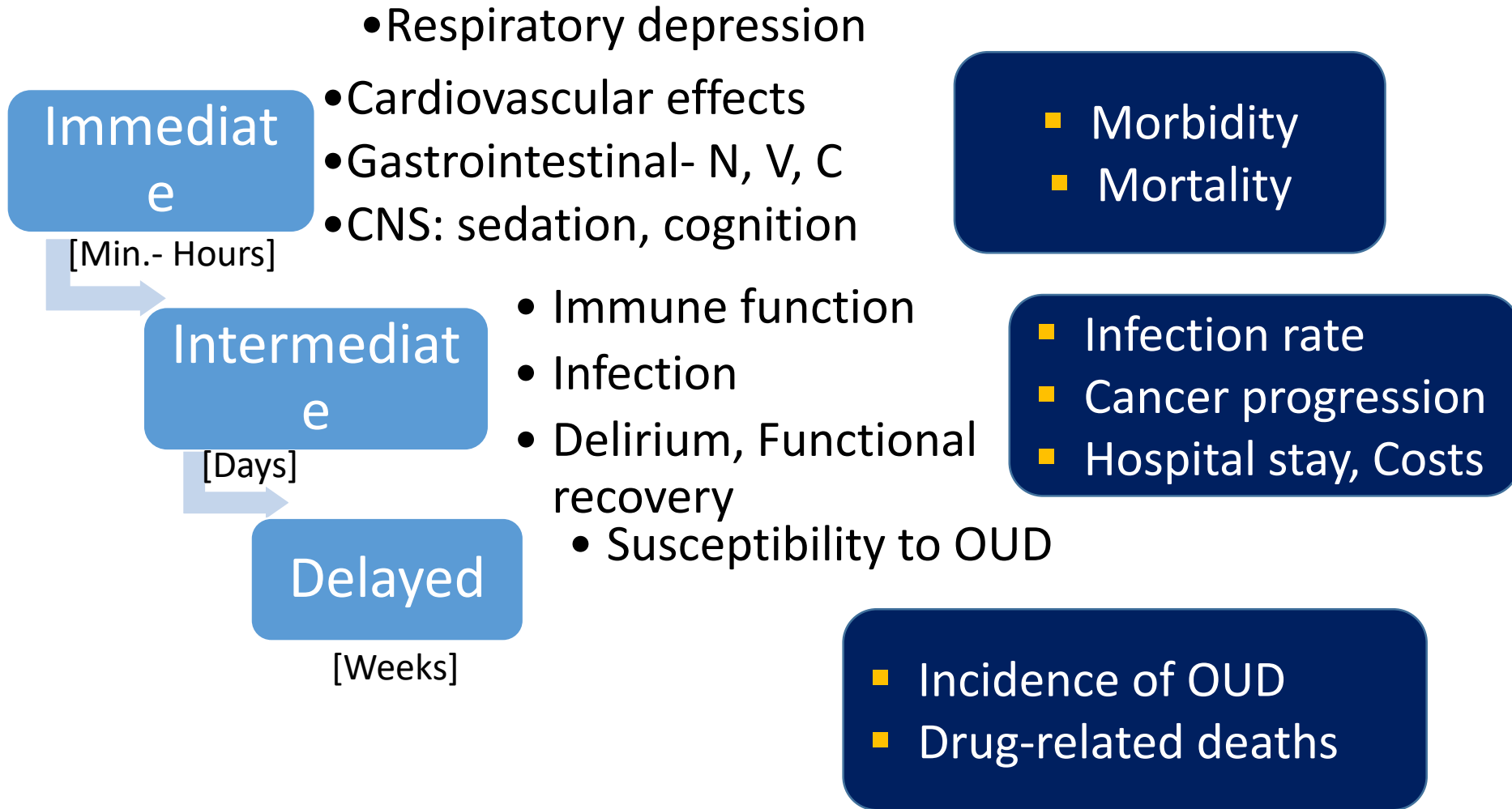
Minkowitz HS et al. J Manag Care Spec Pharm. 2014;20:948-58

Clinical and Economic Burden of Opioid Use for Postsurgical Pain



Barletta JF, Pharmacotherapy 2012;32:12S-18S

Opioids for Acute Pain: What Outcomes may help determine effects of Opioid Sparing Strategies?



Opioids for Chronic Pain: Outcomes to determine beneficial effects of Opioid Sparing Strategies

Immediate

[Min.- Hours]

- Gastrointestinal- N, V, C
- CNS: sedation, cognitive function

- Incidence of AEs
- MVA, Fall injuries
- Overdose death

Intermediate

[Days]

- Immune function, infection
- Endocrine function
- Drug interactions
- Depression

- Infection rate
- Sexual dysfunction
- Depression, suicide

Delayed

[Weeks]

- OIH
- Susceptibility to OUD
- QOL

- Incidence of OUD
- Drug-related deaths

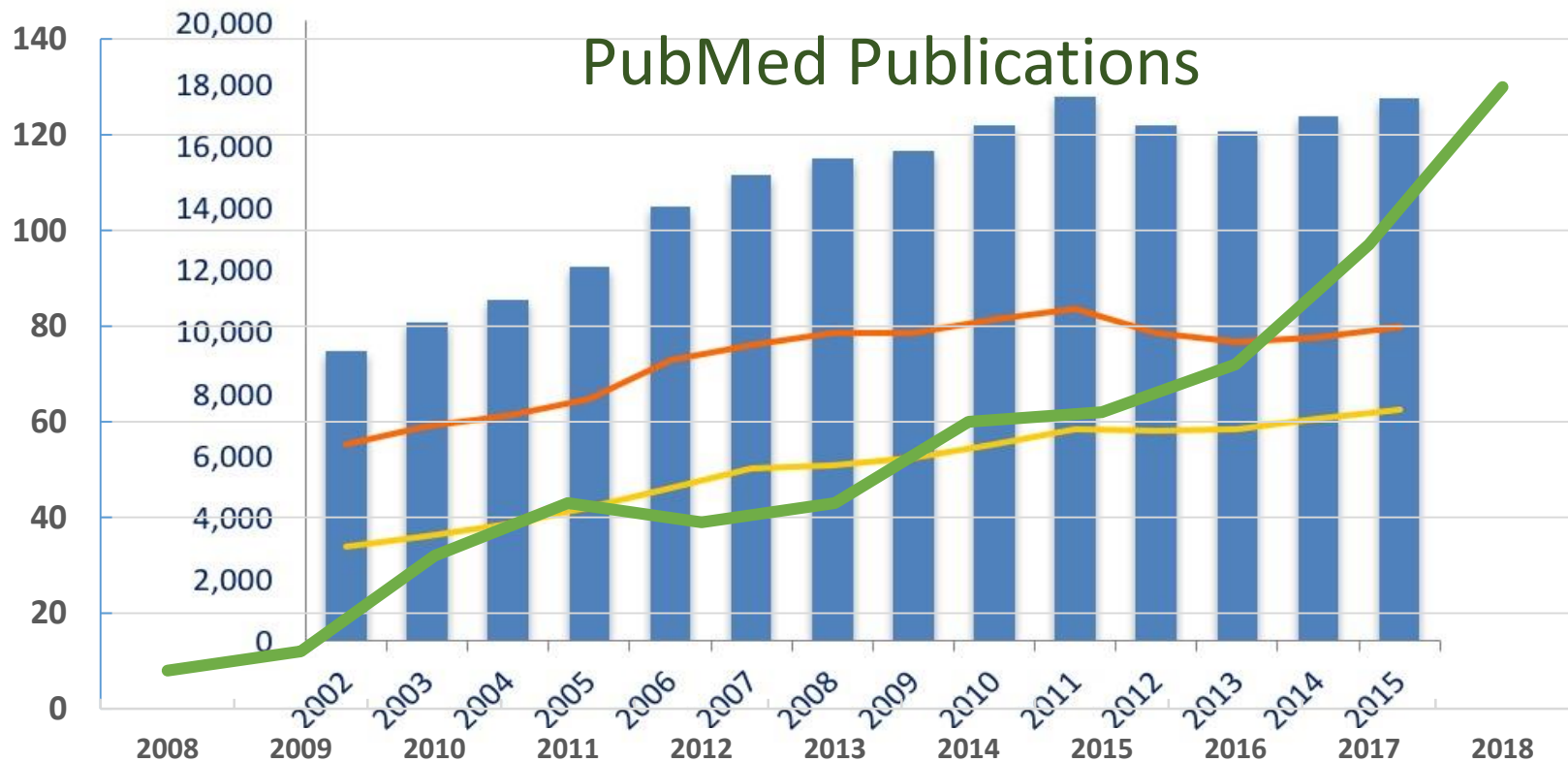
Opioid Sparing AND Pain



National Overdose Deaths

Number of Deaths Involving Prescription Opioid Pain Relievers
(excluding non-methadone synthetics)

■ Total ■ Female ■ Male

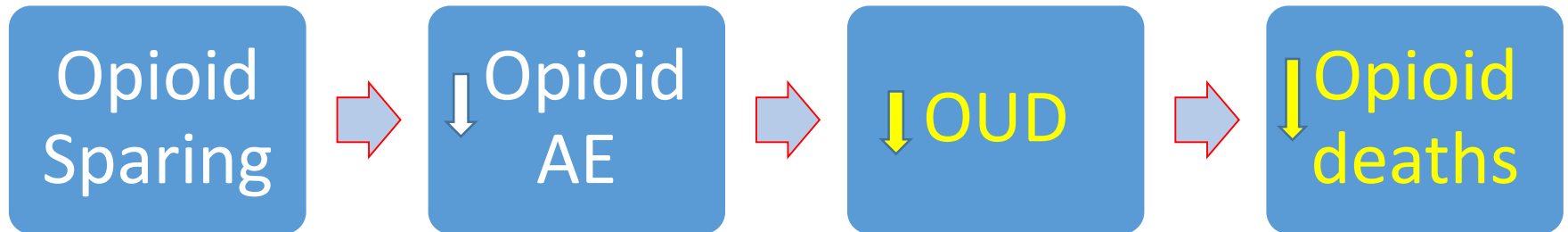


Source: National Center for Health Statistics, CDC Wonder
PubMed Publications

Possible Assumptions and Questions



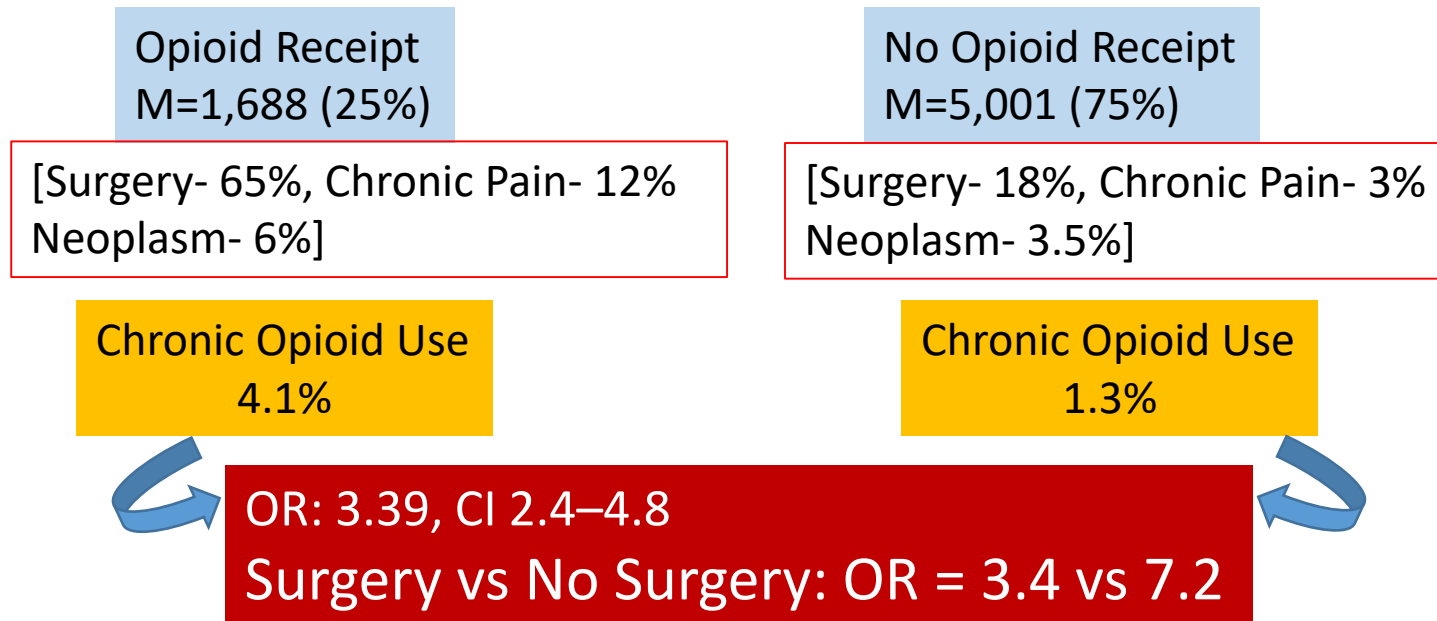
- Opioid use associated adverse effects and deaths are dose-related



- The evidence for relationship between dose and AEs?
- What strategies can help assess if Opioid-sparing will lead to decrease in adverse effects and reduce OUD and opioid-related deaths?
- How to determine a meaningful “sparing” of opioid that will lead to clinically relevant decrease in AEs?

Does Opioid Prescribing at Hospital Discharge Influence Chronic Opioid Use in 'Opioid Naïve' patients?

- Retrospective cohort study, 1 yr hospital admission to an academic center, Denver, n= 6,689
- Opioid prescribing at discharge in opioid-naïve pts. and chronic opioid use (scripts) 1 yr after discharge



What is the incidence of Chronic Opioid Use in Opioid-Naïve Patients after surgery?

- MarketScan-Truven Health Analytics
- 641,941 opioid naïve surgical patients, 2001-13
- 12 m pre- & 12 m post data
- Persistent opioid use:
0.12-1.4% (**0.5%**) vs 0.14% [C]

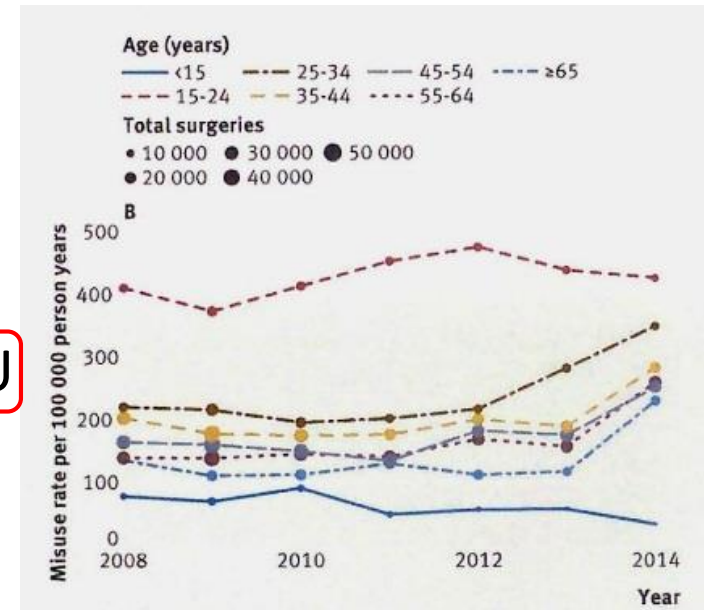
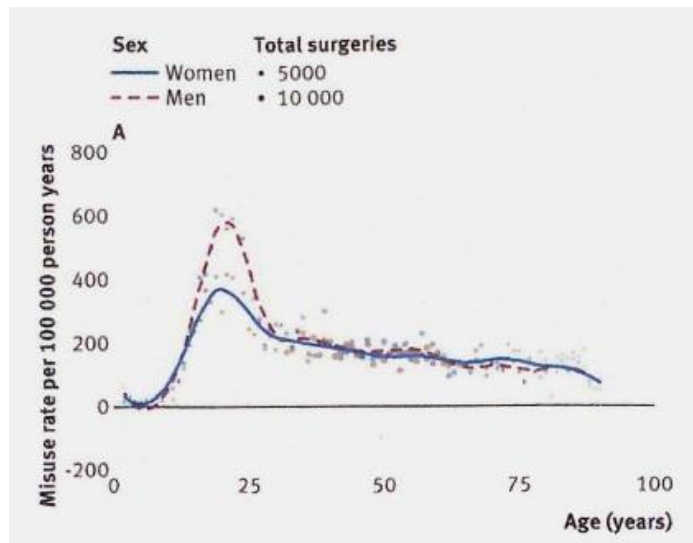
- OptumInsight- Clinformatics Data Mart
- 36,177 opioid naïve surgical patients, 2013-14
- 12 m pre- & 6 m post data
- Persistent opioid use:
5.9 - 6.5% vs 0.4% [C]

- ≥ 10 scripts or >120 d supply
90 d – 12 m after surgery

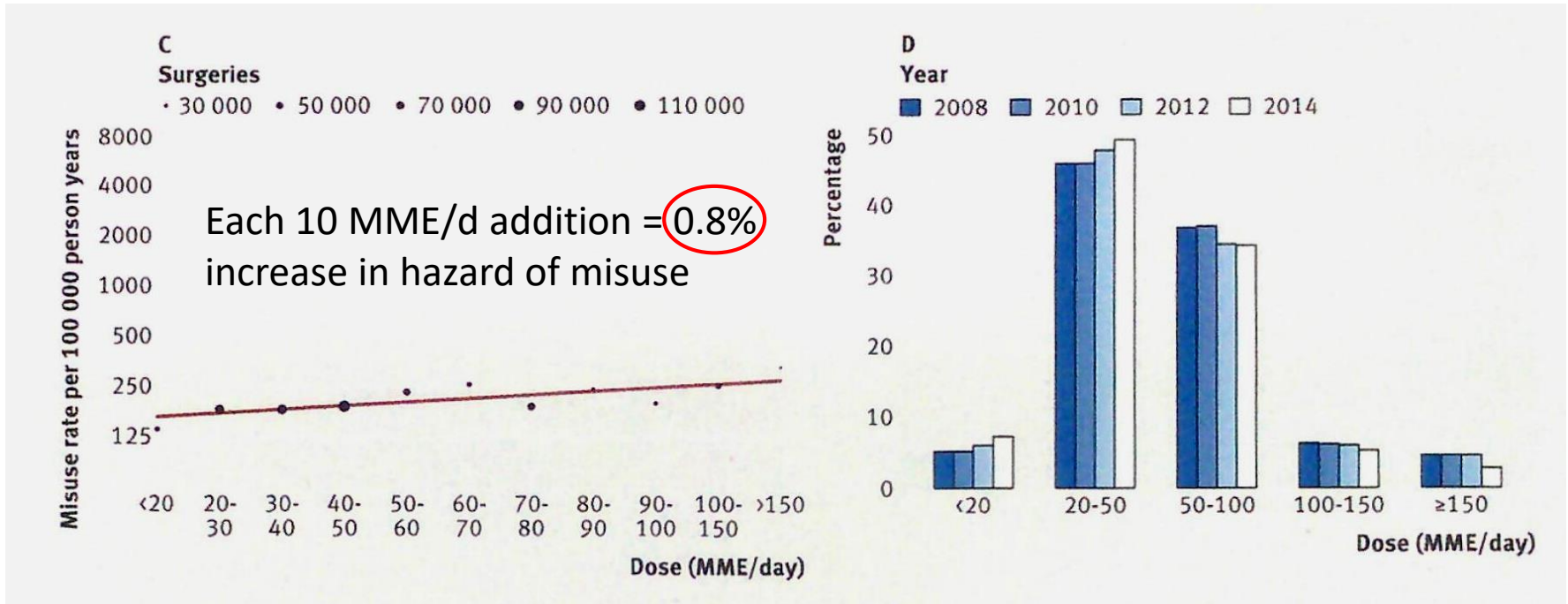
- An opioid Px 90-180 d after surgery

Postsurgical Chronic Opioid Use in opioid-naïve patients: Is there an association between Dose & Misuse?

- Aetna data base- 2008-16,
37.65 million pts- 1 mill. had a surgery
- CPT codes & ICD codes for opioid dependence, abuse, or overdose
- 56.9 K (56%) received postop opioids
- Abuse code- 5.9K (0.6 / 1%), 2.7 yr F/U
- Predictor?

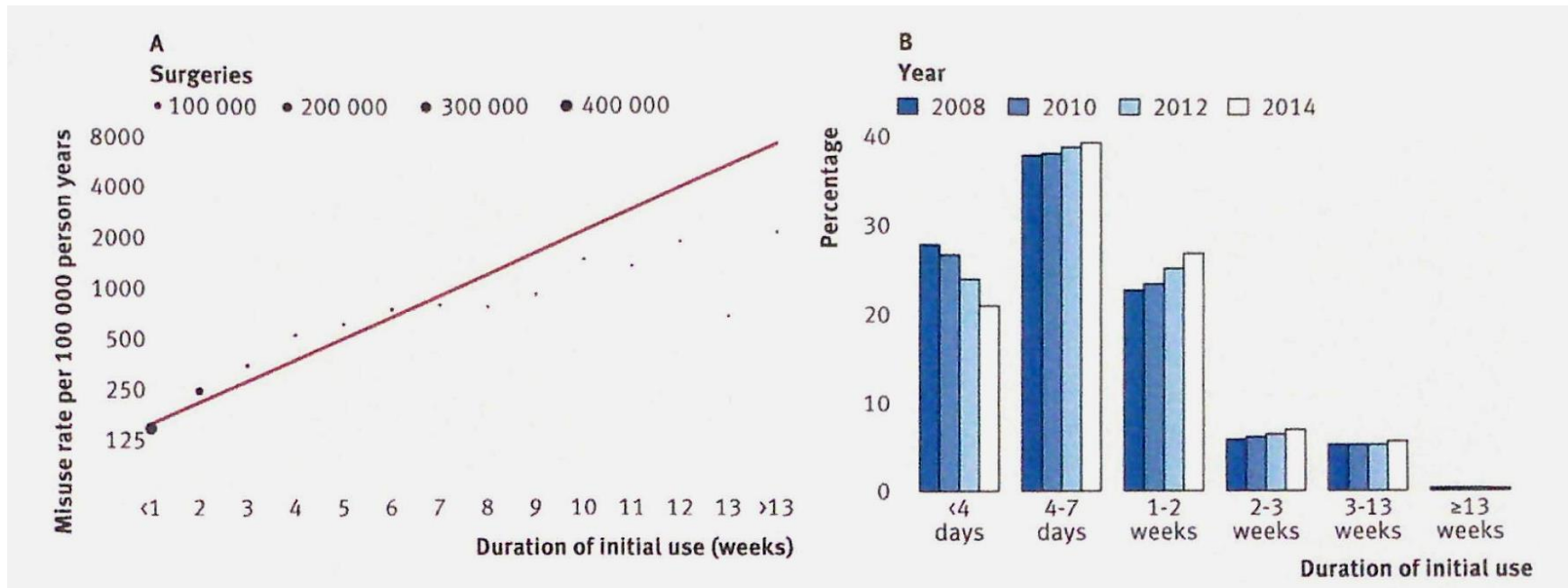


Postsurgical Prescriptions for Opioid-naïve patients: Association with dosage prescribed



Reducing **dose** of postop opioid prescription may have weak effect on lowering incidence of OUD
Is there some other relevant useful indicator?

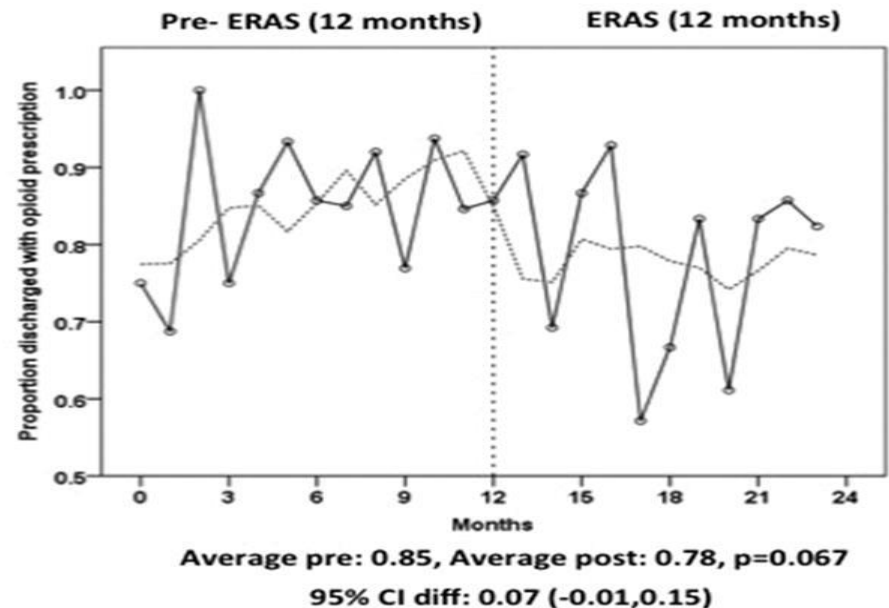
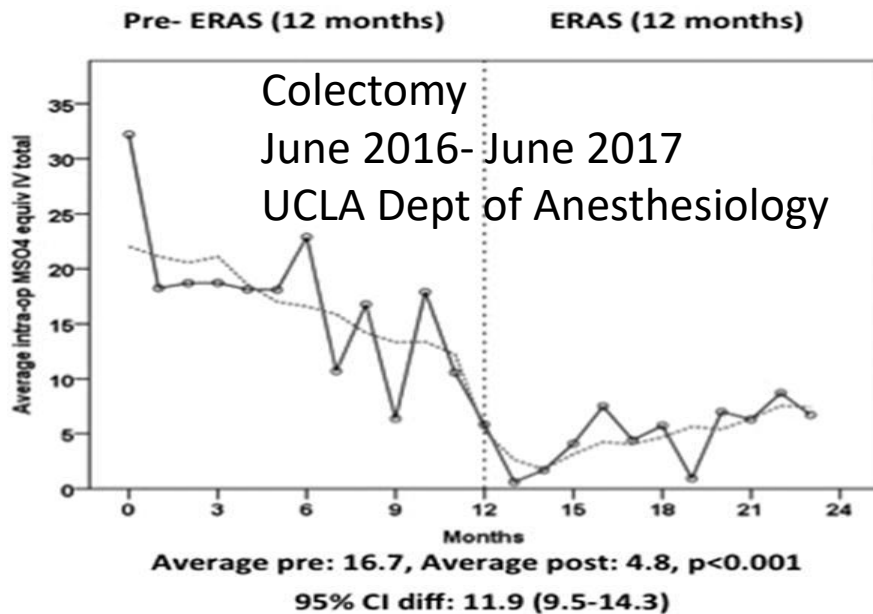
Postsurgical Prescriptions for Opioid-naïve Patients: Association with duration of opioid use post-discharge



“Duration of the prescription rather than the dosage is more strongly associated with ultimate misuse ..”

Limitations: Administrative data, miscoding of abuse, opioid use based on scripts filled- usage?

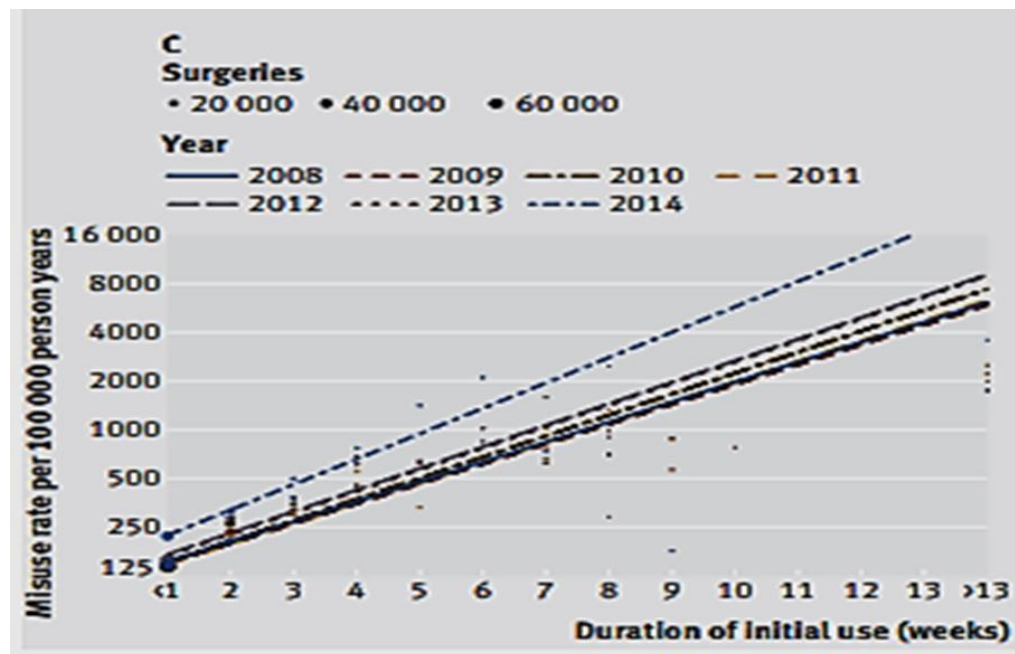
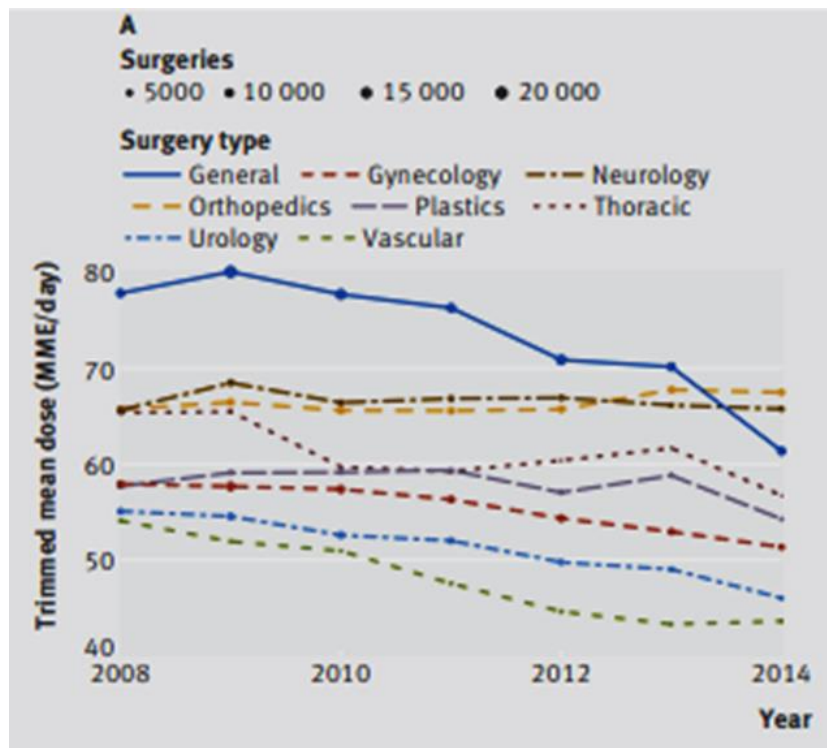
Impact of ERAS and Opioid-Free Anesthesia on Opioid Prescriptions at Hospital Discharge



- Opioid prescription at hospital discharge 85% vs 78% before and after implementation of ERAS implementation
- In hospital “opioid sparing” care does not always result in decreased opioid prescriptions at discharge

A Cause for Pessimism? A reduction in daily opioid use does not alter the misuse rate

Brat AG et al. BMJ 2018;360:j5790

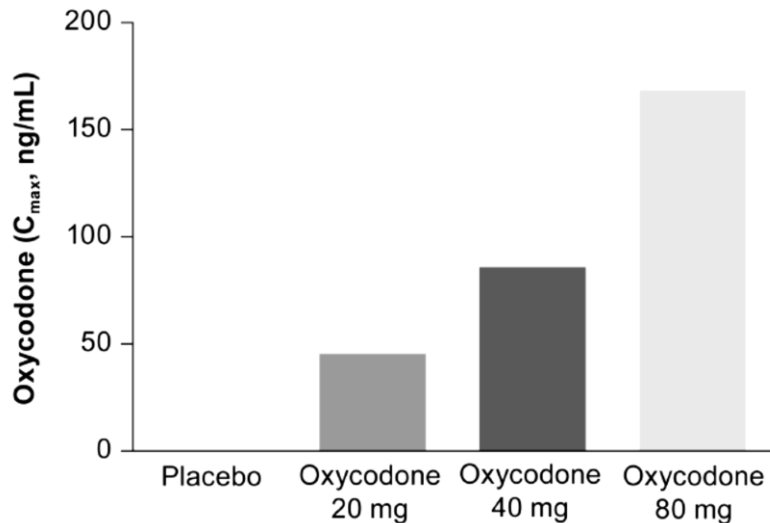


Despite mean opioid dose reduction over time (4-24%), the relation between duration of use and misuse persisted

Does ICD code under estimate? Are patient reports better?

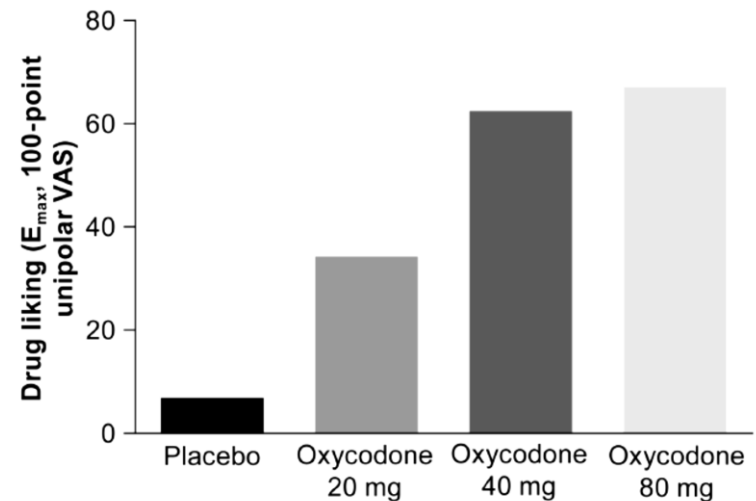
Is Drug Liking Dose-related?

A. Peak plasma oxycodone concentrations



- PK- plasma levels dose-related

B. Peak drug liking



- PD- Plateau effect of drug liking

Instruments to assess patient-reported safety, efficacy, or misuse of .. opioid therapy for chronic pain

Becker WC et al. PAIN 2013; 154:905

Nine Instruments

- **Safety, efficacy, and misuse**
 - Pain Assessment and Documentation Tool (PADT)
 - **Opioid-induced Constipation**
 - Bowel Function index (BFI)
 - Patient Assessment of Constipation Symptoms (PAC-SYM)
 - Bowel Function Diary (BF-Diary)
 - **Misuse**
 - **Current Opioid Misuse Measure (COMM)- 17 Q, 0-4 rating**
 - Prescription Drug Use Questionnaire-patient version (PDUQ-p)
 - Modified Pain Medication Questionnaire (mPMQ)
 - Prescription Opioid Misuse Index (POMI)
 - **Perceived difficulties with opioid therapy**
 - Prescribed Opioid Difficulties Scale (PODS)
- **Equivocal clinical utility**
 - **Not feasible / tested in clinical practice**
 - **Need for trained observers**
 - **Need further development and validation**

Risk Assessment Tools for Prospective Studies

- **Risk of aberrant behaviors** (opioid & substance abuse, opioid dependency, suitability for long term therapy)
 - Opioid Risk Tool (ORT)
 - Screening Instrument for Substance Abuse Potential (SISAP)
 - Diagnosis, Intractability, Risk, Efficacy (DIRE)
 - Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)
- Tools to assess **intentionality of aberrant behaviors** (misuse, abuse, diversion ..)
 - SR-MAD
 - MADDERS

Measures to identify prescription medication Misuse, Abuse, and Related Events [MAREs]:

ACTION- 2013

Smith SM et al. J Pain 2017;18:1287

SR-MAD: Self-Reported Misuse, Abuse, and Diversion instrument

- 15-item pt. self-report instrument (**prospective use only**), maintains **anonymity- ease of use**
- Content validation done in patients with chronic pain-qualitative study (known opioid abuser, non-abuser, naïve)
- Construct & predictive validity and reliability in identifying pts who may misuse or abuse Px-opioid needed
- A new revised measure developed, Prescription Opioid Misuse and Abuse Questionnaire (**POMAQ**)

MADDERS: Misuse, Abuse, and Diversion Drug Event Reporting System

- Can be used **retrospectively & prospectively**
- Triggered by self-report of adverse events and drug accountability discrepancies + **interviewed intent + additional data**
- **Needs trained study staff/adjudicators**
- **Honest answers when faced by staff?**
- Inter-rater reliability, sensitivity, specificity to be tested
- Recommended by **ACTION**

Is there an association between opioid prescribing patterns and overdose-related deaths?

- **Case-cohort design-** association of max. daily opioid dose with risk of opioid overdose death
- 5% random samples of VHA patients (2004 and 2005), and all VHA patients (2004 and 2005), who died of an opioid overdose before the end of FY2008 (“cases”)
- **MEM daily dose** converted to categorical variables: 0, 1 - <20, 20 - <50, 50 - >100 mg, and ≥ 100 mg
- **Patient categories:** Chronic noncancer pain diagnoses, acute pain, cancer diagnoses, Substance use disorder

Higher opioid prescribing patterns may be associated with overdose-related deaths

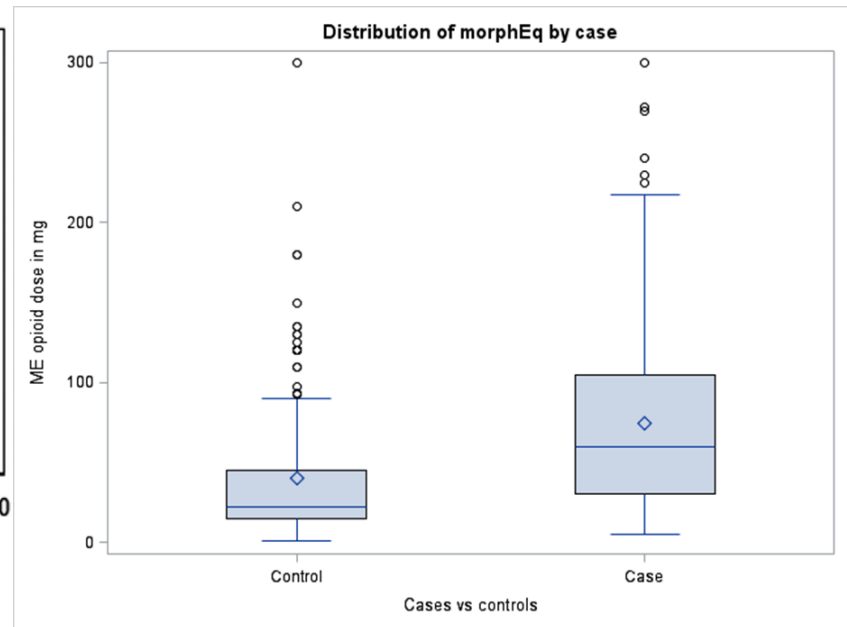
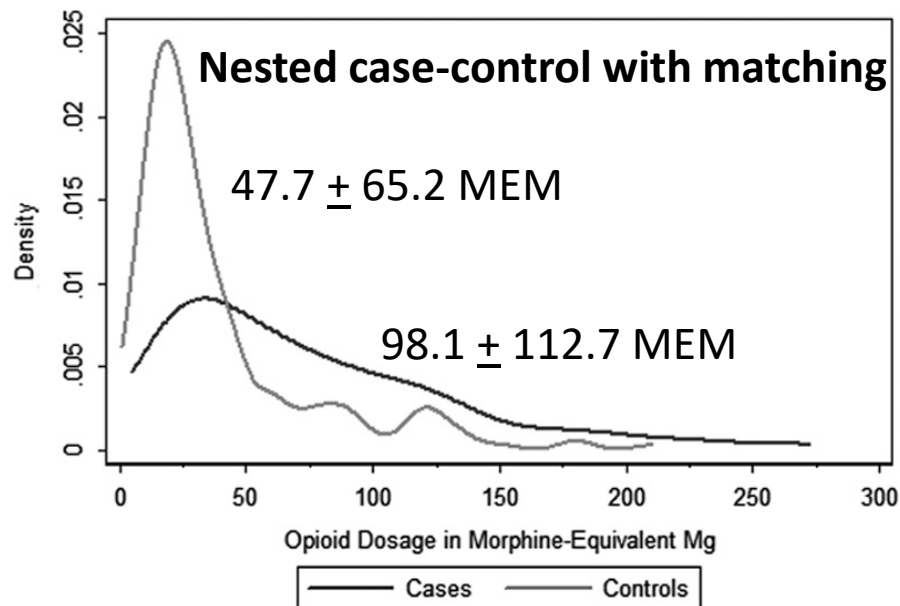
Overdose death rate per 1000 person-months

Maximal opioid dose	0	1- <20	20- <50	50 -<100	>100
Chronic Non-cancer Pain	0.09	0.11	0.24	0.66	1.24
Cancer Diagnosis	0.04	0.08	0.14	0.49	0.98
Acute Pain Diagnosis	0.12	0.21	0.36	1.13	1.82
Substance Use Disorder Diagnosis	0.42	0.54	0.78	1.59	2.97

Frequency of fatal overdose = 0.4%

Risk of overdose death correlated with maximal Px daily dose of opioid medication

Prescribed Opioid Dosage and Overdose Deaths in Patients with Chronic Pain- VHA observational study



- A clear cut-point in opioid dosage to distinguish between overdose cases and controls was not found
- Lowering recommended dosage threshold <100 MEM .. would affect ..**few** patients not at risk for overdose while potentially benefitting **many** of those at risk for overdose.”

Summary

The delicate balancing act:

Optimal pain relief with minimal adverse effects



- Acute Pain Management- Acute adverse effects mostly dose-related and “opioid-sparing may be beneficial”
 - Periop. opioid sparing is \neq low opioid prescription at discharge
- Chronic opioid use in opioid naïve patients related to *duration* of Px post surgery- “opioid-sparing” needs to consider dose and duration of therapy
- Patient-reported measures to detect MAREs need further validation to test sensitivity and specificity
- Little quantitative data to indicate *how much* of a reduction in opioid dose will lead to meaningful reduction in OUD, Death