What do we know about long-term opioid efficacy and safety?

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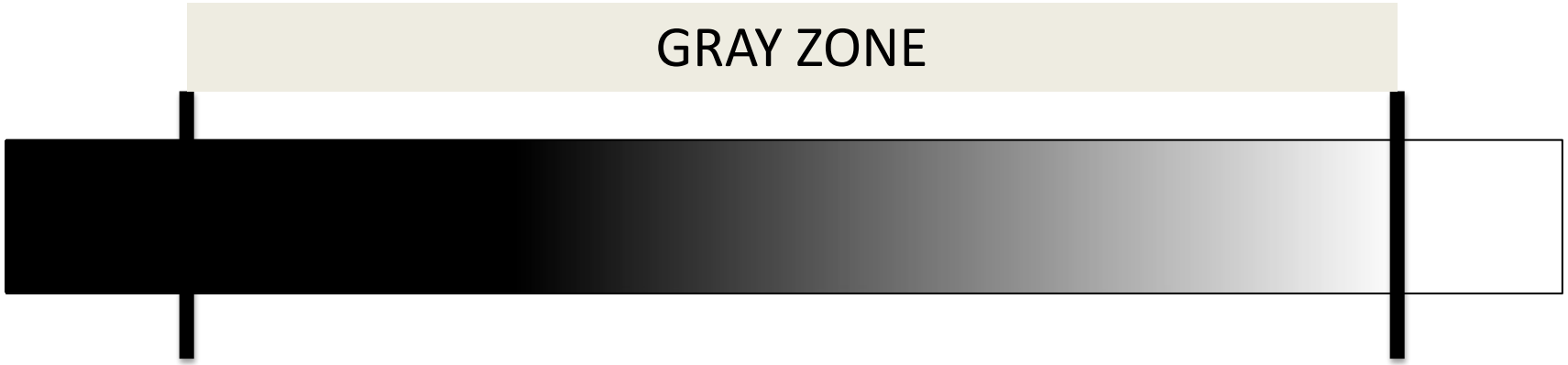
Why does dependence cause opioid treatment failure

What is the evidence that supports efficacy and safety for chronic opioid therapy

Does dose make a difference



ADDICTED

Meets DSM criteria for addiction

NOT ADDICTED

- No lost prescriptions
- No ER visits
- No early prescriptions
- No requests for dose escalation
- No UDT aberrancies
- No doctor shopping (PMP)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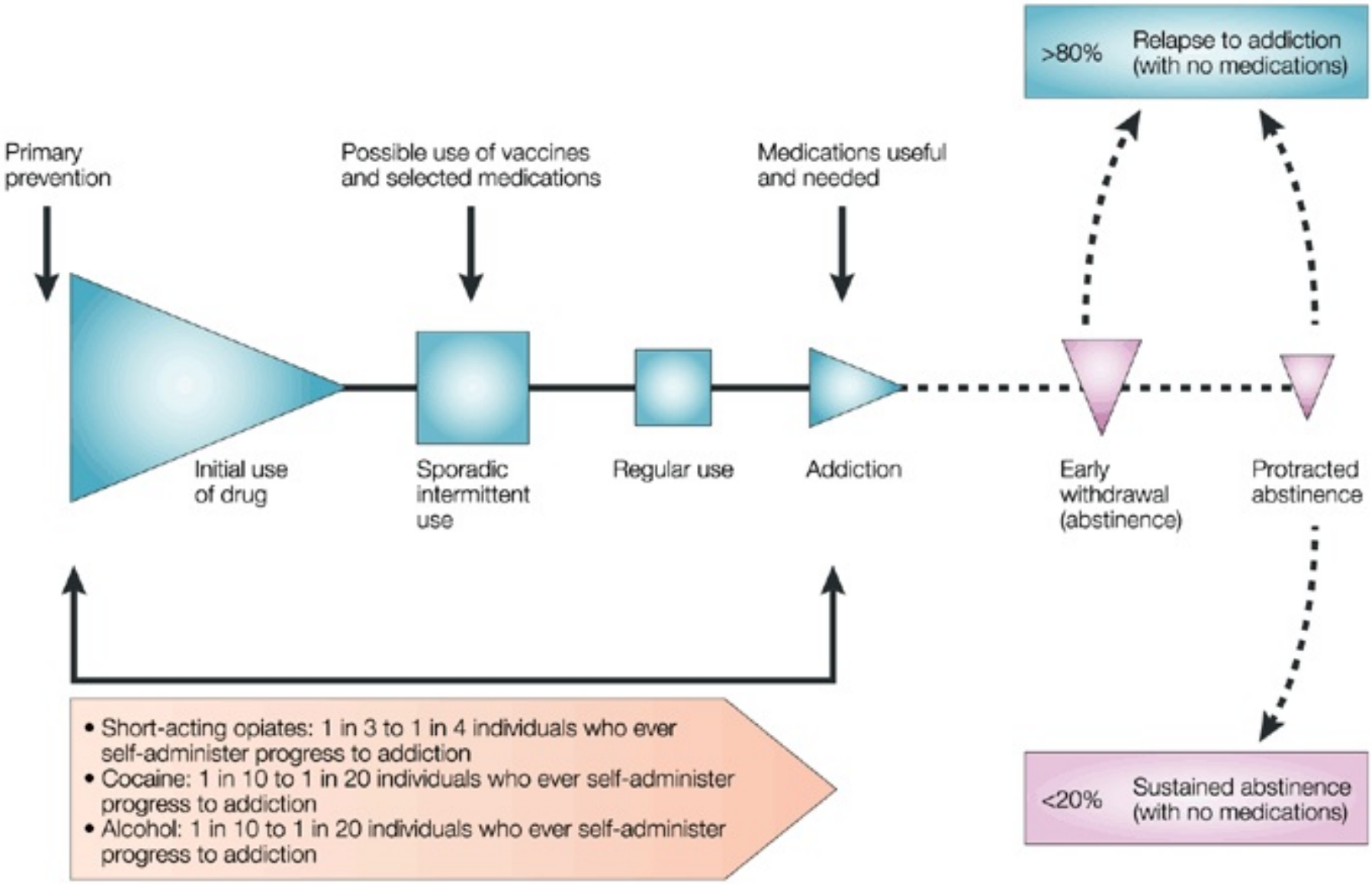
Treasurer of the United States.



Kreek, LaForge & Butelman Nat Rev Drug Discov 2001;1:710-26

DSM V Behavioral criteria for Substance Use Disorder

A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by 2 or more of the following:

- Failure to fulfill major role obligations at work, school or home
- Continue in situations in which it is physically hazardous (eg driving)
- Persistent or recurrent social or interpersonal problems
- Substance taken in larger amounts or longer than was intended
- Persistent desire or unsuccessful efforts to cut down
- Great deal of time spent in activities necessary to obtain substance, use substance or recover from substance use
- Important social, occupations or recreational activities given up or reduced
- Continued use despite knowledge of harm
- Craving

Opioid seeking behaviors

Dependence/addiction develops through pain treatment

- Need opioid to treat pain
- Using opioid to cope
- Pestering reluctant doctors
- Predominant symptom of withdrawal - pain

Dependence/addiction develops through recreational drug use

- Need to procure opioid
- Often use paraphernalia
- Predominant symptom of withdrawal - anhedonia

DSM Criteria

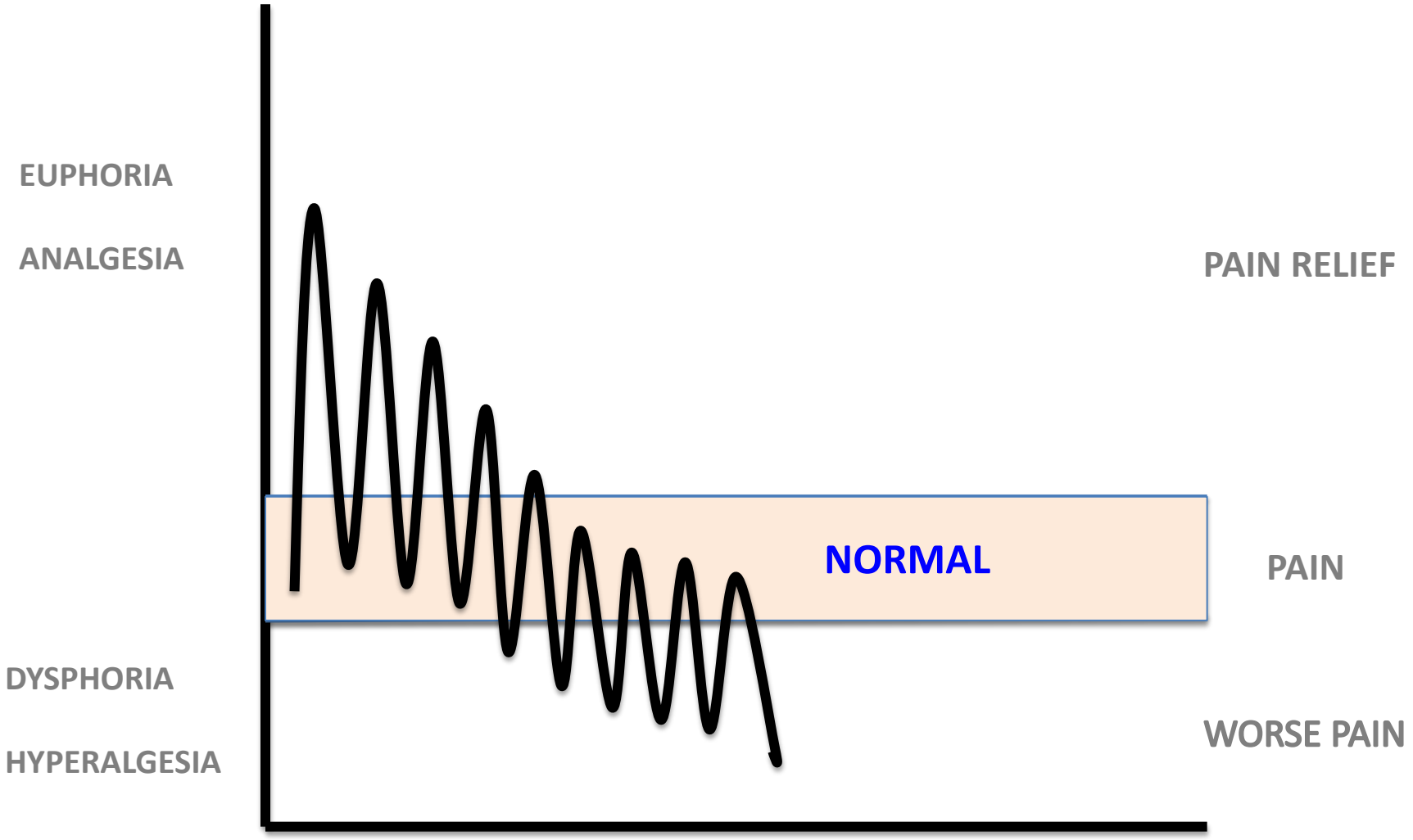
- Social Disruption
- Loss of control over use
- Continued use despite knowledge of harm
- (Craving)

(may not be manifest until off)

Do not accept that anything is wrong other than pain

Accept that they are addicted

What we understand about opioid dependence



Dependence is inevitable with continuous use

- Physical – regions of control of somatic function - locus ceruleus (noradrenergic nucleus)

  upregulation of cAMP $\longleftrightarrow$ *arousal, agitation, diarrhea, rhinorrhea, piloerection*

- Emotional/psychological – reward centers

  hedonia $\longleftrightarrow$ *anhedonia*

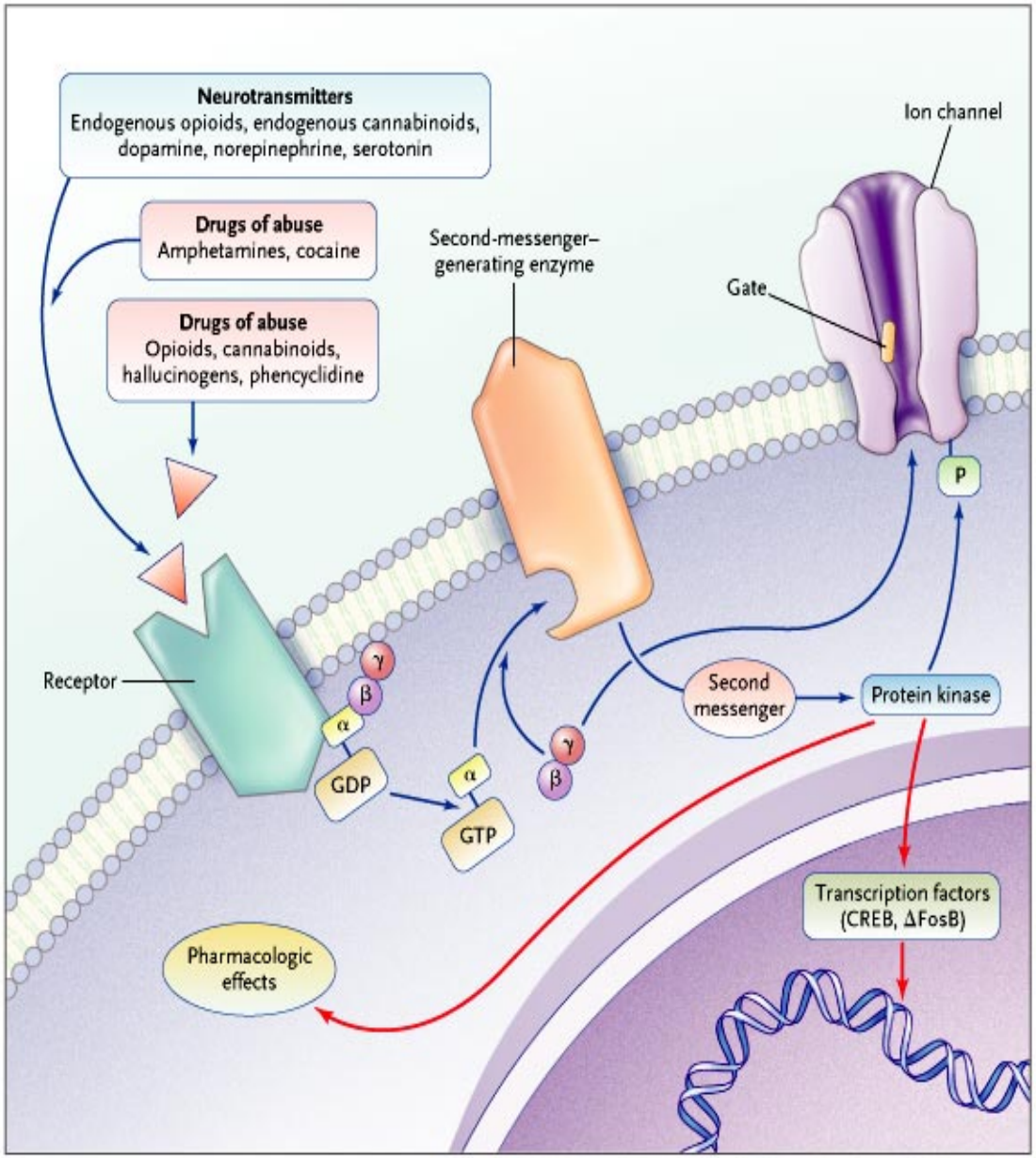
- Pain pathways

  analgesia $\longleftrightarrow$ *hyperalgesia*

Ballantyne & LaForge, Pain 2007;129:235
Ballantyne et al, Arch Int Med 2012;172:1342

Enduring adaptations

- Explain relapse
- Result of complex interactions between drugs themselves and the circumstances under which they are taken
- Neuroadaptation occurs through gene regulation, remodeling of circuits, changes in intrinsic excitability, increased in synaptic strength, actual morphological changes
- These adaptations may also alter analgesia and tolerance



Metabotropic Mechanisms of Action of Drugs of Abuse

Cami, J. et al. N Engl J Med 2003;349:975-986

Enduring adaptations produced by established behaviors

For the illicit drug user:

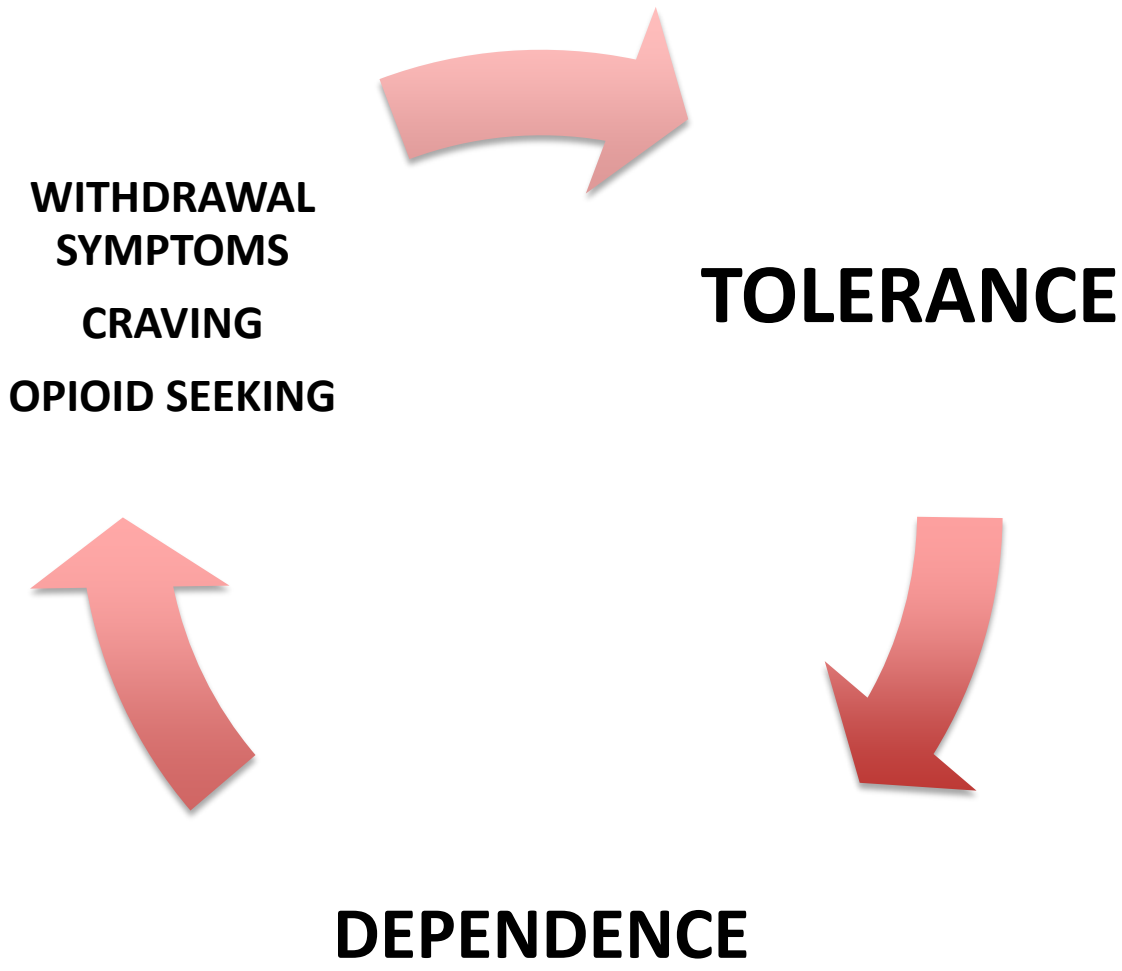
- Procurement behaviors

For the pain patient – much more complex:

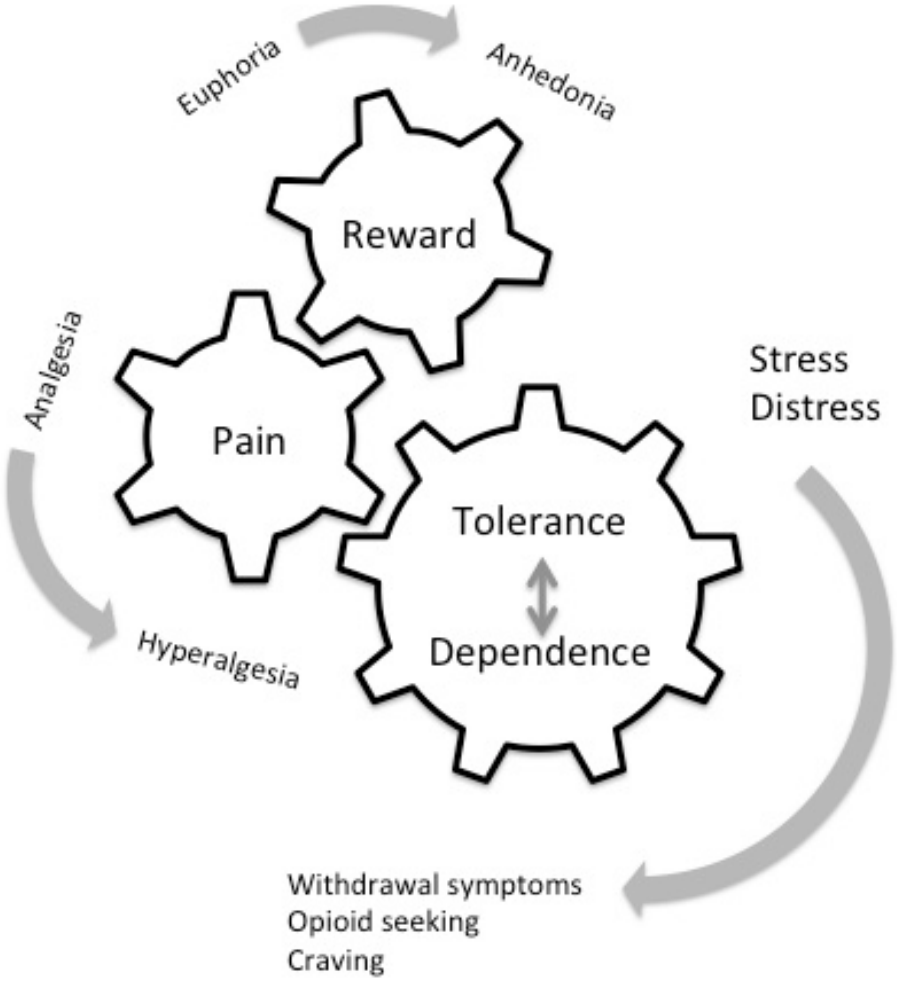
- Continuous opioid therapy may prevent opioid seeking
- Memory of pain, pain relief and possibly also euphoria
- Even if the opioid seeking appears as seeking pain relief, it becomes an adaptation that is difficult to reverse
- It is hard to distinguish between drug seeking and relief seeking

- Tolerance is the need to increase dose to achieve the same effect
- Tolerance may develop for both the euphoric and analgesic effects of opioids
- Tolerance can be produced by both psychological (associative) and pharmacological (non-associative) factors

Ballantyne & LaForge Pain 2007;129:235


WITHDRAWAL SYMPTOMS
CRAVING
OPIOID SEEKING
TOLERANCE
DEPENDENCE

- Pain patients taking opioids continuously and long-term inevitably develop tolerance and dependence
- Psychosocial stressors not only increase pain, but also increase tolerance
- Doses are increased to avoid withdrawal and worsening pain
- Ultimately leads to the patient for whom no dose is enough



Ballantyne et al Arch Int Med 2012;172:1342

Summary points

- Patients who stay on opioid pain treatment long-term and continuously will inevitably develop dependence
- Dependence is not simply physical, nor is it easily reversed
- Distinguishing dependence from addiction is not easy in the setting of pain treatment with opioids
- Dependence requires treatment similar to addiction

What is the evidence that supports efficacy and safety for chronic opioid therapy

Current evidence

Observational

- Clinical case series and open label follow up studies support efficacy and safety of opioids
- Generally doses are low to moderate and length of treatment is 1-2 yrs, pain relief is partial
- No conclusion on function or quality of life
- *Many people who are started on opioids discontinue* either because of adverse effects or inadequate pain relief

Epidemiological

- For wider population, analgesic effectiveness is not substantiated
- Function of opioid treated patients seems poor, opioid treated pain patients are less likely to work than non-treated matched cohorts
- Lack of safety of opioids has been revealed, especially for high doses (death, fracture, endocrine effects)
- Beginning to understand how many dose escalate (most of those that stay on)
- Beginning to understand who dose escalates (*adverse selection*)

Ballantyne JC. Clinical and administrative data review presented to FDA May 30th and 31st 2012. 2012.

OBSERVATIONAL DATA

Portenoy and Foley
Chronic use of opioid analgesics in non-malignant pain: report of 38 cases
Pain 1986;25:171-86

- 38 pts
- 24 good pain relief, 14 inadequate, 2 control issues
- 19 pts > 4 yrs, 6 pts > 7 yrs
- Dose 2/3 < 60 MED, only 4 pts > 120 MED
- Diagnoses: 14 back, 9 facial, abdominal, pelvic and extremity, others a hodgepodge

Ballantyne & Shin
Efficacy of opioids for chronic pain: a review of the evidence
Clin J Pain 2008;24:469-78

11 case series found in the literature (includes Portenoy)

Majority report treatment up to 2 yrs at doses up to 195 MED

There are some outliers: Tennant et al 1988 report on treatment up to 40 yrs at doses > 2000 MED; Zenz et al 1992 report treatment > 4 yrs at doses > 2000 MED

Usually report satisfactory analgesia at stable doses with low risk of addiction

Most report improvements in function but through patient reports of function

Noble et al
Long-term opioid management for chronic non-cancer pain
Cochrane Database Syst Rev 2010;1

25 case series or open label continuation studies (all prospective)

Included several newer studies published since 2008

Oral in 12 (n=3040), transdermal in 5 (n=1628)

High discontinuation rates (for oral 23% for adverse effects, and 10% for inadequate analgesia) (similar to other studies)

Most report significant pain relief, but findings on function and quality of life are inconclusive

Not possible to assess addiction risk or predictors

Most are conducted for up to 1 yr (exception Portenoy et al 2007 up to 3 yrs, Mystakidou et al 2003 up to 4 yrs)

Dose differences were not considered by this review

Summary of observational data

- Generally achieve improvement in pain
- Although there are a few outliers, generally these patients are followed for no more than 2 yrs
- Doses are moderate (up to 200 MED), with a few outliers (> 2000 MED)
- Findings on function and quality of life are equivocal
- No conclusions on addiction risk

EPIDEMIOLOGICAL DATA

Eriksen et al
Critical issues on opioids in chronic non-cancer pain: An epidemiological study
Pain, 2006;125:172-9

228 opioid users compared with 1,678 non-opioid users

Opioids usage significantly associated with:

- reporting of severe pain
- poor self-rated health
- inactivity during leisure
- unemployment
- higher healthcare utilization
- poor health orientated quality of life on SF-36

SUMMARY – EPIDEMIOLOGICAL DATA

- For wider population, analgesic effectiveness is not substantiated
- Function of opioid treated patients seems poor, opioid treated pain patients are less likely to work than non-treated matched cohorts
- Lack of safety of opioids has been revealed, especially for high doses (death, fracture, endocrine effects)
- Beginning to understand how many dose escalate (most of those that stay on)
- Beginning to understand who dose escalates (adverse selection)

- Epidemiological data include all the patients who have dose escalated and are not doing well

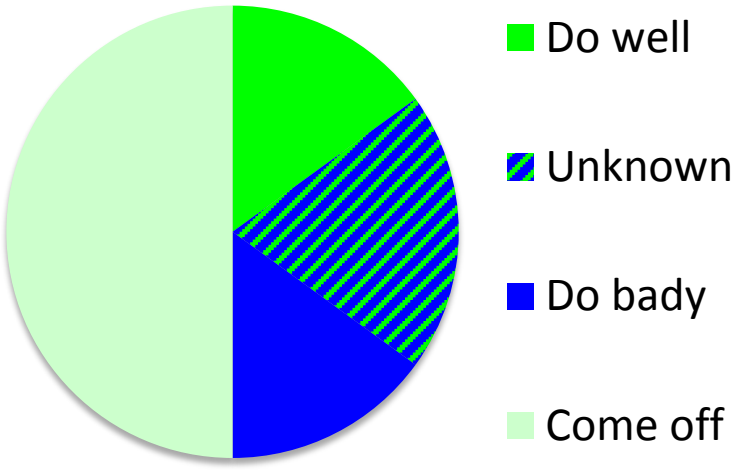
- They include all the patients who are not treated in the careful practice settings that are typical of case series and open label follow up studies

- Since the 1980s, opioids are being used for an increasing range of patients and diagnoses (wider range than described by Portenoy and Foley 1986, Tennant et al 1988 and Zenz et al 1992)

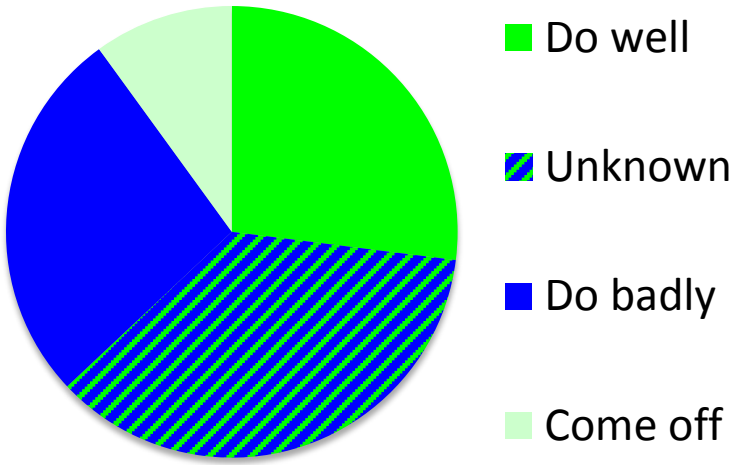
Toblin et al A population-based survey of chronic pain and its treatment with prescriptions drug Pain 2011;152:1249-55
Sjorgen Epidemiology of chronic pain and critical issues on opioid use Pain 2011;6:1219-20

Why populations look worse than published cohorts

Cohort of patients who start on opioids



Population of patients at a given time point



REVIEW

Annals of Internal Medicine

The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop

Roger Chou, MD; Judith A. Turner, PhD; Emily B. Devine, PharmD, PhD, MBA; Ryan N. Hansen, PharmD, PhD; Sean D. Sullivan, PhD; Ian Blazina, MPH; Tracy Dana, MLS; Christina Bougatsos, MPH; and Richard A. Deyo, MD, MPH

Systematic Review prepared for NIH Pathways to Prevention Workshop

Summary findings:

- No study of opioid therapy versus no opioid therapy evaluated long-term (>1yr) outcomes related to pain, function, quality of life, opioid abuse or addiction
- Good- and fair-quality observational studies suggest that opioid therapy for chronic pain is associated with increased risk for overdose, opioid abuse, fractures, myocardial infarction and markers of sexual dysfunction (few studies of each)
- For some harms, higher doses are associated with increased risk
- Evidence on the effectiveness and harms of different opioid dosing and risk mitigation strategies is limited

What is the accuracy of screening instruments?

3 studies (2 fair quality, 1 poor quality) reported very inconsistent estimates of diagnostic accuracy precluding reliable conclusions

Table 5. Predictive value of risk assessment instruments

Scale	Studies	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	AUROC
DIRE	Moore, 2009[113]	Score <14: 0.17	Not calculable[a]	Not calculable[a]	Not calculable[a]	Not calculable[a]
ORT	Jones, 2012[112]	Score >4: 0.20 (95% CI 0.15 to 0.27)	Score >4: 0.88 (95% CI 0.82 to 0.93)	Score >4: 1.65 (95% CI 0.78 to 3.51)	Score >4: 0.91 (95% CI 0.78 to 1.06)	0.53
	Moore, 2009[113]	Score >4: 0.45	Not calculable[a]	Not calculable[a]	Not calculable[a]	Not calculable[a]
	Webster, 2005[109]	Score ≥4: 0.99 (95% CI 0.92 to 0.999)	Score ≥4: 0.16 (95% CI 0.10 to 0.24)	Score ≥4: 0.99 (95% CI 0.92 to 0.999) Score 1-3: 0.08 (95% CI 0.01 to 0.62) Score 4-7: 0.57 (95% CI 0.44 to 0.74) Score ≥8: 14.34 (95% CI 5.35 to 38)	Score ≥4: 0.16 (95% CI 0.10 to 0.24)	Not reported
PMQ	Jones, 2012[112]	Score >30: 0.34 (95% CI 0.20 to 0.51)	Score >30: 0.77 (95% CI 0.69 to 0.80)	Score >30: 1.46 (95% CI 0.87 to 2.45)	Score >30: 0.86 (95% CI 0.68 to 1.08)	0.57
SOAPP-R	Jones, 2012[112]	Score >17: 0.39 (95% CI 0.26 to 0.54)	Score >17: 0.69 (95% CI 0.63 to 0.75)	Score >17: 1.27 (95% CI 0.86 to 1.90)	Score >17: 0.88 (95% CI 0.70 to 1.10)	0.54
SOAPP	Moore, 2009[113]	Score ≥6: 0.73	Not calculable[a]	Not calculable[a]	Not calculable[a]	Not calculable
	Akbik, 2006[108]	Score ≥8: 0.68 (95% CI 0.52 to 0.81)	Score ≥8: 0.38 (95% CI 0.29 to 0.49)	Score ≥8: 1.11 (95% CI 0.86 to 1.43	Score ≥8: 0.83 (95% CI 0.50 to 1.36	Not reported

[a]Retrospective study; only patients who had discontinued opioids due to aberrant drug-related behavior were included.

What is the effectiveness of risk mitigation strategies on outcomes related to overdose, addiction, abuse or misuse, including:

1. Opioid management plans
2. Patient education
3. Urine drug screening
4. Use of prescription monitoring data
5. Use of monitoring instruments
6. More frequent monitoring intervals
7. Pill counts
8. Use of abuse deterrent formulations

No studies

Does dose make a difference

Doses > 100 mg MED are a red flag

- Pain is not responsive
- Insurmountable tolerance (no dose is enough)
- Difficulty controlling use
- Misuse
- Addiction
- Diversion

1.Morasco BJ, Duckart JP, Carr TP et al *Pain.* Dec 2010;151(3):625-632.
2.Edlund MJ, Martin BC, Fan MY et al *Drug Alcohol Depend.* Nov 1 2010;112(1-2):90-98.
3.Weisner CM, Campbell CI, Ray GT, et al. *Pain.* Oct 2009;145(3):287-293.

Longer duration and higher dose associated with

- Higher rates of overdose and death
- Less likelihood of being able to wean if necessary
  - Difficulty controlling acute pain, surgical recovery, terminal pain
  - Continued use during pregnancy – neonatal abstinence
- Higher rates of mental health & substance use disorder, less able to control usage
- Higher rates of falls and fractures in the elderly
- Less likelihood of returning to function or work
- Higher rates of endocrinopathy affecting fertility, libido & drive
- Higher rates of immune dysfunction

1. Dunn KM, Saunders KW, Rutter CM, et al. *Ann Intern Med.* Jan 19 2010;152(2):85-92.
2. Martin BC, Fan MY, Edlund MJ et al *J Gen Intern Med.* Dec 2011;26(12):1450-1457.
3. Miller M, Sturmer T, Azrael D et al *J Am Geriatr Soc.* Mar 2011;59(3):430-438.
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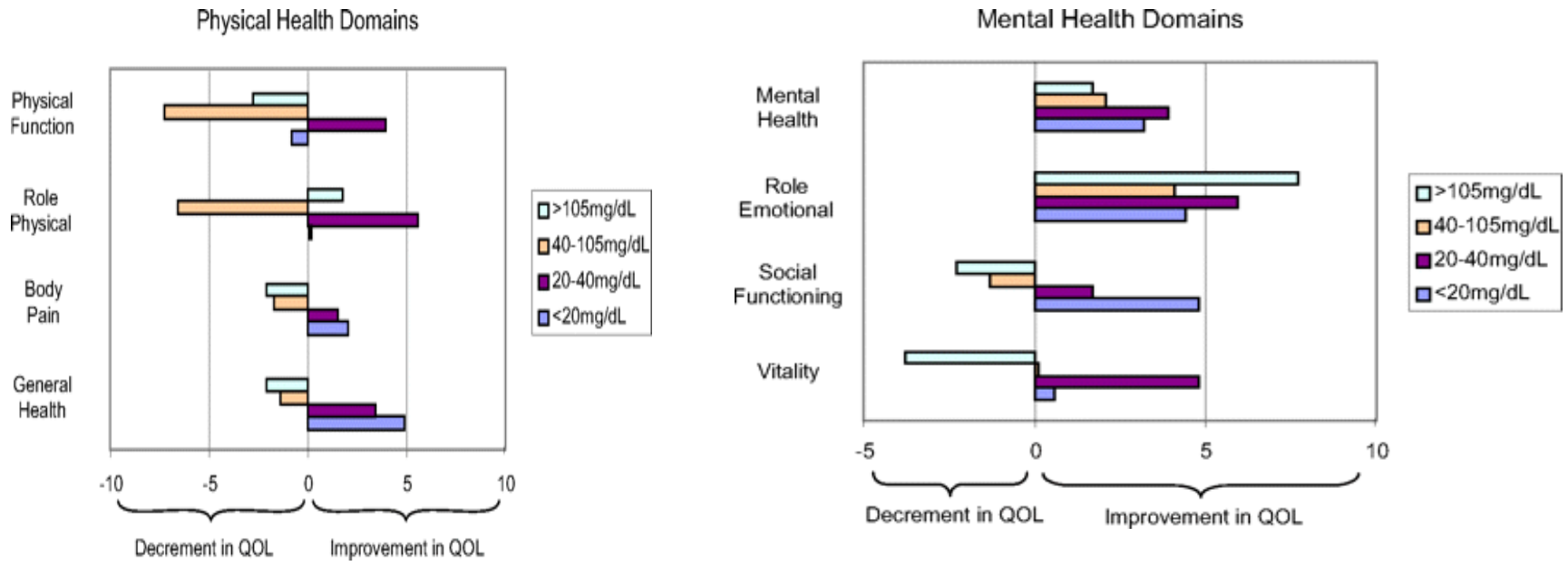
Dillie et al
Quality of life associated with daily opioid therapy in a primary care chronic pain sample
J Am Board Fam Med 2008;21:108-17

Propensity score adjusted difference in SF-36 physical and mental health domain scores vs. non-opioid users



801 daily opioid users vs 93 matched non-opioid chronic pain patients recruited from the practices of 235 PCPs, divided into low, moderate and high-dose groups

OPIOIDS, FUNCTION AND RETURN TO WORK

Webster et al 2007 after controlling for covariates (including injury severity), mean disability duration, mean medical costs, risks of surgery and later opioid use all increase with MED

Franklin et al 2008 after adjustment for pain, function, injury severity and other baseline covariates, > 7 days opioid and > 1 prescription is associated significantly with work disability at 1 yr

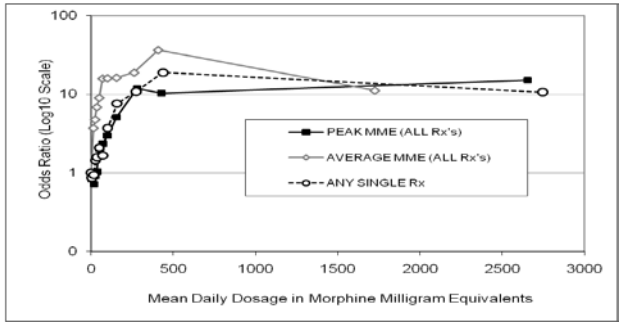
Gross et al 2009 early opioid prescription and delayed recovery are associated, but likely explained by pain severity and other confounders

Volinn et al 2009
- odds of chronic work loss 11-14 times higher for pts with opioid prescriptions at <90 days
- costs $19,453 higher
- strong association suggests that opioid did not arrest the cycle of work loss and pain

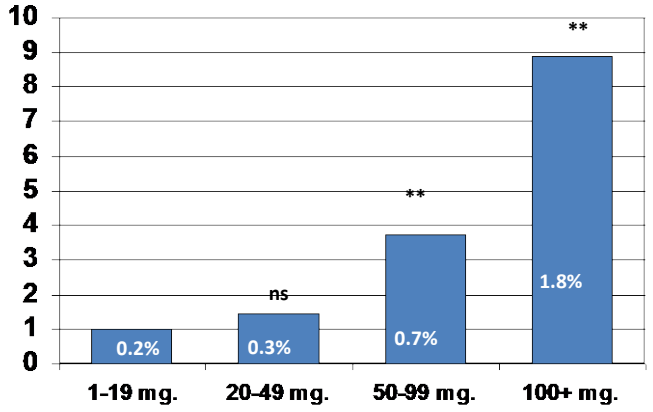
Webster et al Spine 2007;32:2127-32
Franklin et al Spine 2008;33:199-204
Gross et al Spine 2009;35:525-31
Volinn et al Pain 2009;142:194-201

DEATHS AND HIGH DOSES

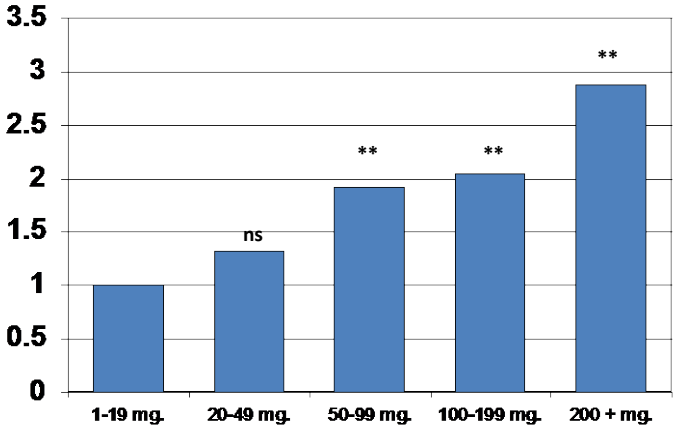
Crude association of daily dosage of opioid analgesics with risk of unintentional drug overdose death, New Mexico, October, 2006—March, 2008



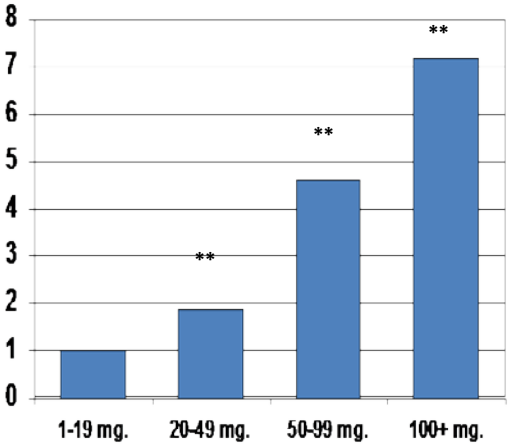
Paulozzi , et al. Pain Med 2012; 13:87-95



Dunn et al., Annals Int Med, 2010

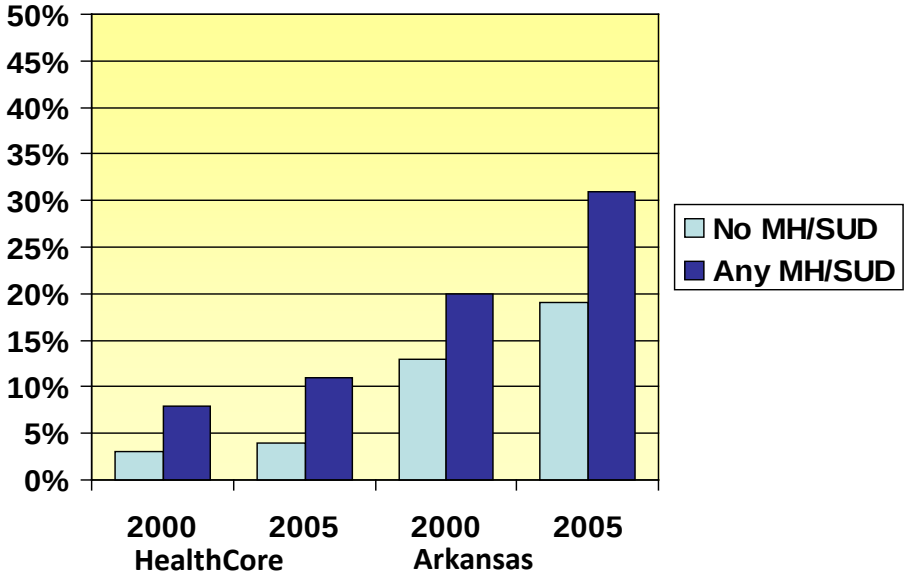


Gomes et al., Arch Int Med, 2011



Bohnert et al., JAMA, 2011

ADVERSE SELECTION



Chronic opioid use (>90d/yr) in patients with MH and SUD diagnoses

Edlund et al Drug Alcohol Depend 2010; 112:90-98

Schwartz et al 2006;45:136-142
Sullivan et al Arch Intern Med 2006;166:2087-93
Edlund et al Pain 2007;129:355-362
Weisner et al Pain 2008;145:287-93
Edlund et al Clin J Pain 2010;26:1-8
Martin et al J Gen Intern Med 2011;26:1450-7
Phifer et al Pain 2011;152:2233-40
Seal et al JAMA 2012;307:

CONCLUSIONS

Problems seem to be centered on high dose users*

Safety data are compelling, and even though causation cannot be proved, this evidence has to be factored into any assessment of effectiveness

Lack of convincing data on efficacy for high dose opioids is an additional reason to state that on the basis of current evidence, effectiveness (benefit vs risk) of high dose opioids is not proven

*safety begins to decline at > 50 MED, safety markedly declines at >100 MED

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