

REVIEW OF THE EVIDENCE FOR THE EFFICACY AND EFFECTIVENESS OF OPIOID ANALGESICS FOR CHRONIC PAIN

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OBSERVATIONAL DATA

RANDOMIZED TRIALS

EPIDEMIOLOGICAL 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

Notable: all treated in a cancer center, nearly all were compliant

A PATIENT

Judith Brown is a 32 yr old with pain associated with juvenile arthritis



Pain relief remains inadequate after multiple treatment attempts, including primary disease treatment and non-opioid analgesics

Pain is interfering with her function and she is miserable; she has not worked for 3 months

She is considered a suitable candidate for opioid treatment of chronic pain



She has a good response to opioid therapy

One year later she reports improved function

Pain score is reduced from 9/10 to 6/10

She reports renewed energy and enjoyment and she is able to work again

What evidence is there in the literature that supports this clinical impression?

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
- Many people who are started on opioids discontinue either because of adverse effects or inadequate pain relief

OBSERVATIONAL DATA

RANDOMIZED TRIALS

EPIDEMIOLOGICAL DATA

Randomized Controlled Trials (RCTs)

Inclusion criteria

- Adults \geq 18yr
- Pain \geq 4 on a 0-10 scale
- Moderate or severe pain
- Pain not adequately controlled by NSAIDs or COX-2 inhibitors

Study designs

- Parallel double-blind
- Cross-over
- Enriched enrollment
 - Placebo and/or active comparator
- Usually 4-12 wk treatment periods

Kalso E, Edwards J, Moore R, McQuay H

Opioids in chronic non-cancer pain: systematic review of efficacy and safety

Pain 2004;112:327-80

- 15 RCTs (4 IV) strong opioids vs. placebo (1025 pts)
- The mean decrease in pain intensity in most studies was at least 30% with opioids and was comparable in neuropathic and musculoskeletal pain
- About 80% of patients experienced at least one adverse event, with constipation (41%), nausea (32%) and somnolence (29%) being most common
- In open-label follow-up studies, only a minority (44%) of patients achieved significant long lasting analgesia for between 7 and 24 months with tolerable adverse events

Opioids and Chronic non-cancer pain in older adults: Systematic review & meta-analysis

- Opioid vs Placebo or add-on Rx (Mean age ≥ 60 yr)
 - 18 RCTs, 78% excellent methodology score
 - Significant reductions in pain intensity and physical disability, non-significant changes in sleep and QOL

| Outcome | Studies | Subjects Opioid / Placebo | Placebo mean change | Opioid Mean change | Mean Δ Effect (ES) (P-value) |
|----------------------|---------|---------------------------------|---------------------------|--------------------------|---|
| PAIN | 18 | 3005 / 1865 | - 0.68 | -1.25 | -0.55 (<0.001) |
| PHYSICAL FUNCTION | 9 | 1822 / 935 | -0.57 | -1.0 | -0.43 (0.001) |

Papaleontiou M. J Am Geriatr Soc 58;1353:2010

ES= Active- Placebo

Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E
Opioids for chronic non-cancer pain: a meta-analysis of effectiveness
and side effects *Can Med Assoc J* 2006;174:1589-94

- 41 RCTs and 6019 patients
- Included weak opioids (eg tramadol)
- Treated for up to 16 weeks
- Weak and strong opioids outperformed placebo for pain and function in all types of CNCP
- Other drugs produced better functional outcomes than opioids, whereas for pain relief they were outperformed only by strong opioids
- Despite the relative shortness of the trials, **more than 1/3 abandoned treatment because of lack of efficacy**

Summary of RCT findings and limitations

- Randomized short duration efficacy studies using various trial designs show that, compared to placebo, opioids significantly decrease nociceptive and neuropathic pain
- The efficacy of opioids in nociceptive and neuropathic pain is similar
- Length of treatment up to 8 months
- Doses moderate (up to 180 mg/day morphine)
- No conclusion on tolerance and addiction (patients at risk of addiction excluded)
- No systematic assessment of function

Ballantyne & Mao NEJM 2003;349:1943, Kalso et al Pain 2004;112:372, Furlan et al CMAJ 2006;174:1589

Missing

Does the analgesia last?

Does the treatment improve function and quality of life?

What is the risk of addiction?

OBSERVATIONAL DATA

RANDOMIZED TRIALS

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:

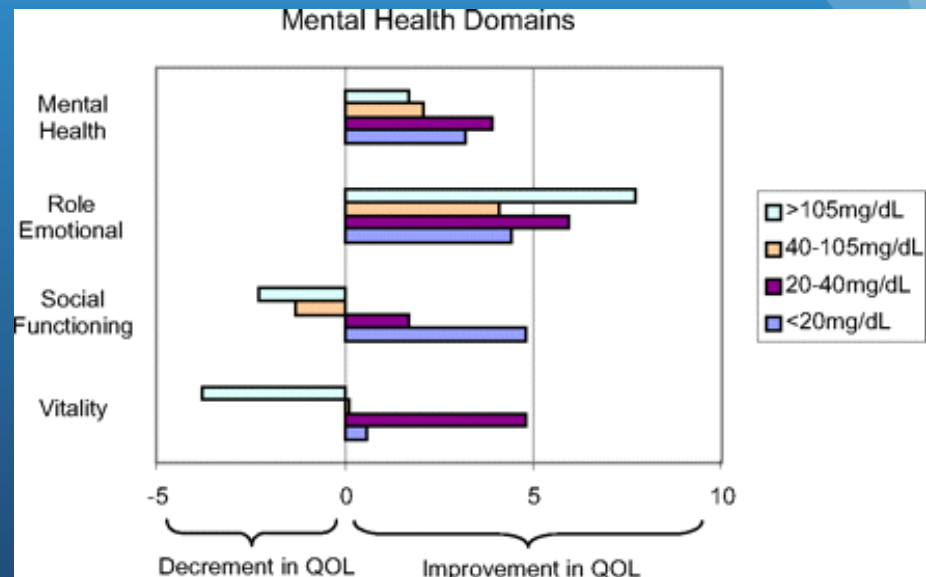
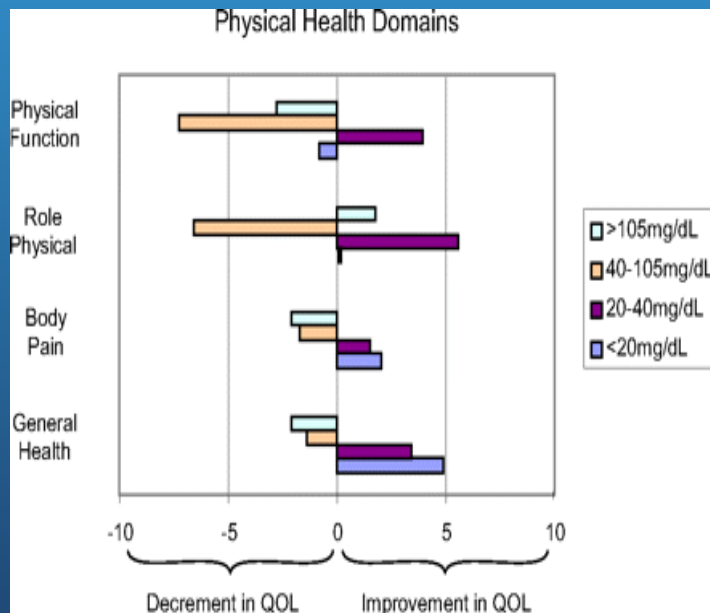
- reporting of severe pain
- poor self-rated health
- inactivity during leisure
- unemployment
- higher healthcare utilization
- poor health orientated quality of life on SF-36

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

OUR PATIENT

2 yrs after she started opioids and experienced good pain relief and important functional improvement, she has a hard time getting through the winter. Her mother's health is deteriorating, and she needs to take on her care. She has had to give up her job and goes on disability.

She states that the pain relief she is now getting is not as good as it used to be, and she requests a dose increase.

In the ensuing 4 yrs, requests for dose escalation become more frequent, and neither pain relief nor function are as good as they were. She has been told that her disease has 'burned out'.



After 6 yrs

Daily opioid dose is now 500 MED

Pain is 10/10

She is virtually house-bound

She is finding it hard to get out of bed in the morning

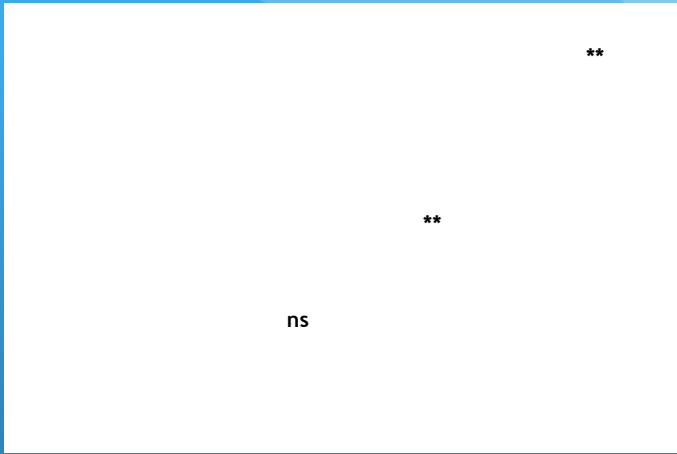
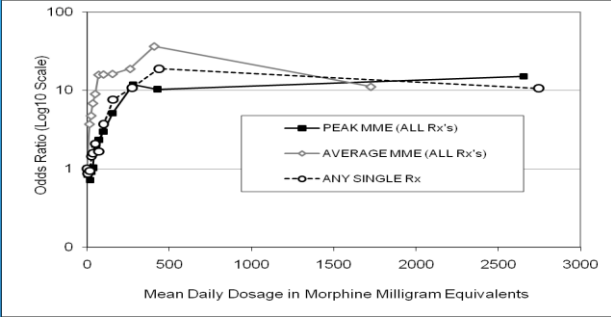
Her mother has died

Nothing is helping

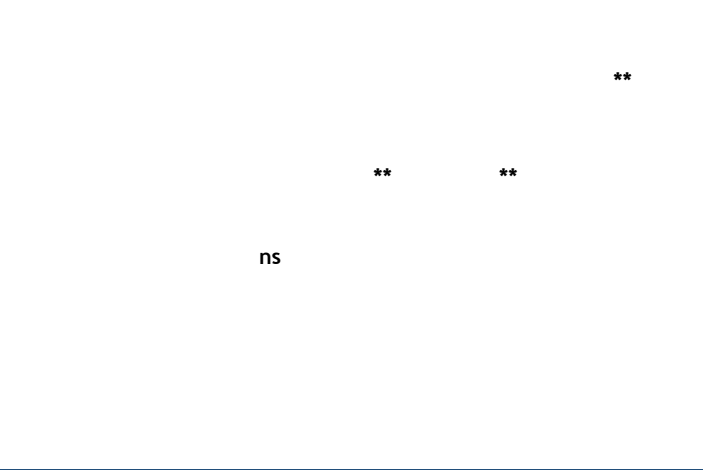
Why dose matters, and what the epidemiological data have revealed about high doses

DEATHS AND HIGH DOSES

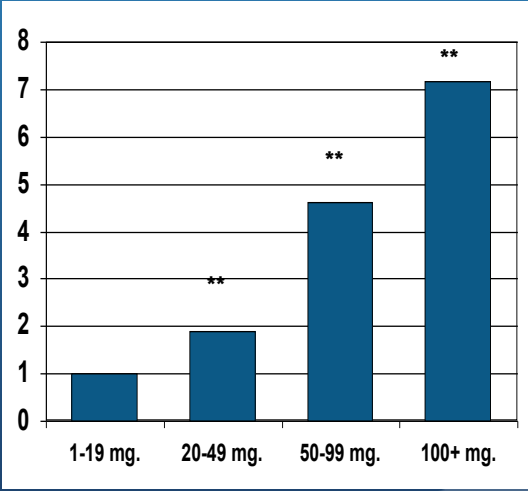
Crude association of daily dosage of opioid analgesics with risk of unintentional drug overdose death,
 New Mexico, October, 2006 March, 2008



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

OPIOIDS, FUNCTION AND RETURN TO WORK

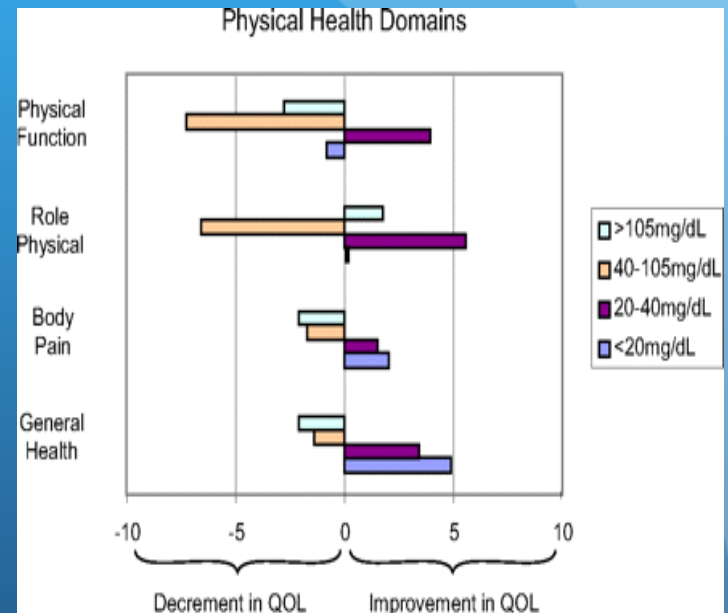
Relationship to high dose

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

Dillie et al 2008 All health domains deteriorate rather than improve at > 40 mg MED, and the only improvement for higher doses are in emotional and mental health

Kidner et al 2009 Both high dose groups (61-120 and >120 mg MED) are significantly related to lower rates of return to work and work retention, higher healthcare utilization and higher disability

CONSORT data 56% of lower dose users (<50 mg MED) are working compare to 39% of moderate dose users (50-99 mg MED) and 36% of higher dose users (>100 mg MED)

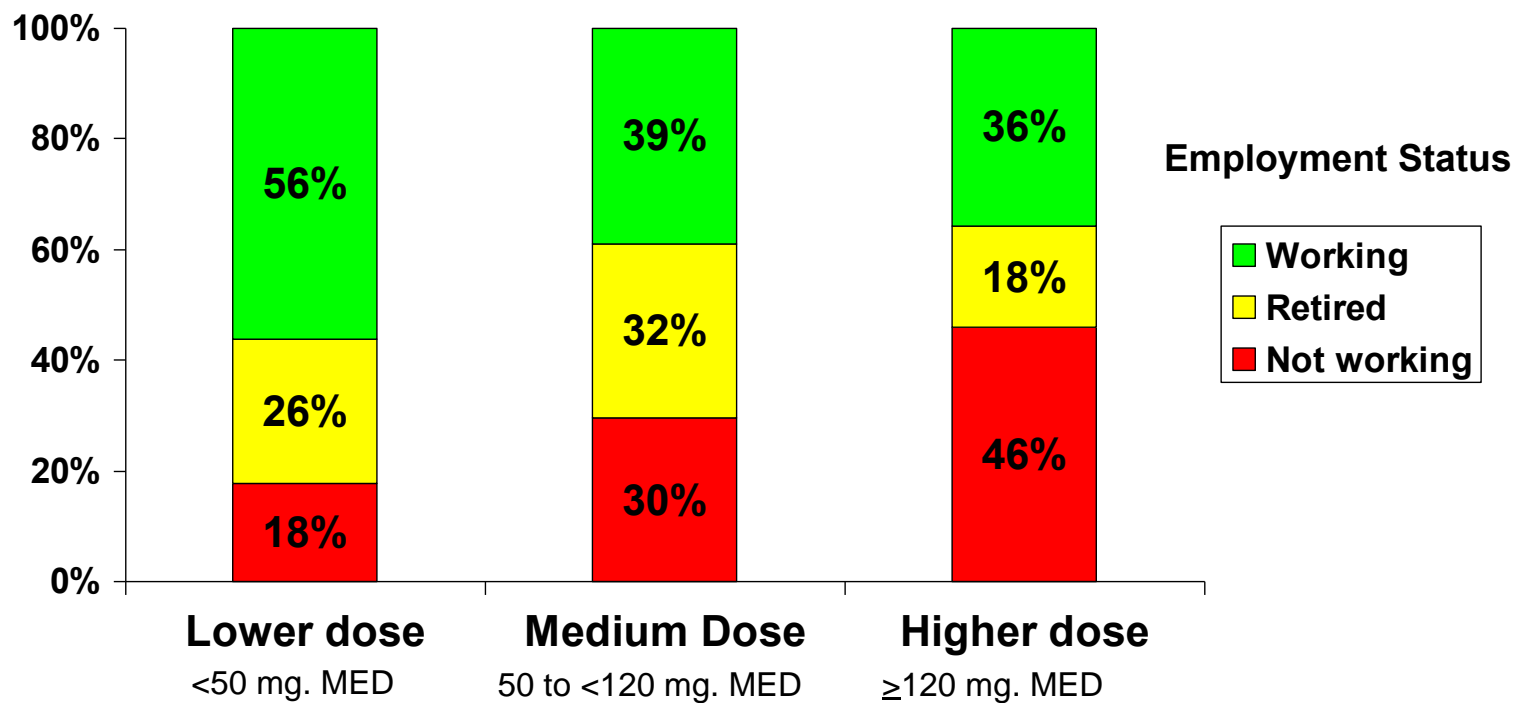


Webster et al Spine 2007;32:2127-32

Dillie et al, J Am Board Fam Med 2008;21:108

Kidner et al, J Bone Joint Surg Am 2009;91:919

Employment Status COT Patients by Average Daily Dose



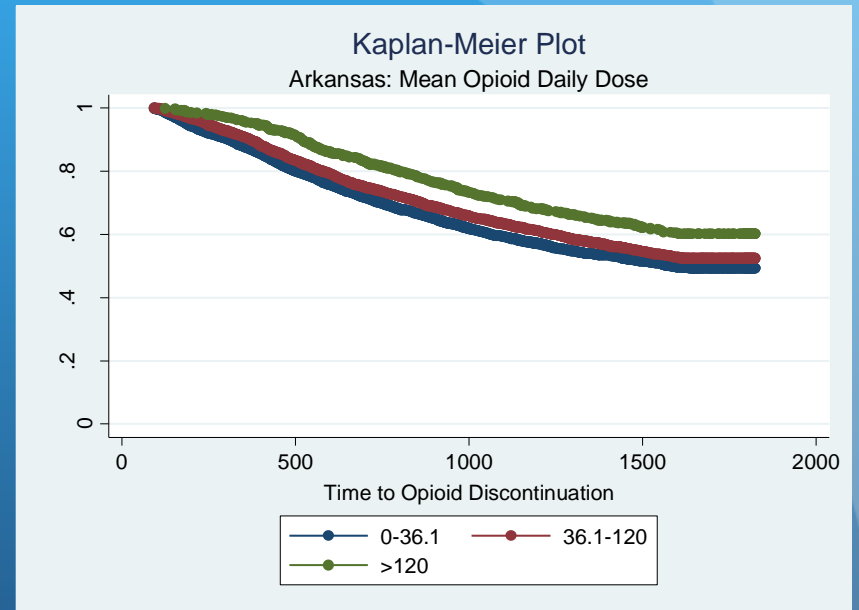
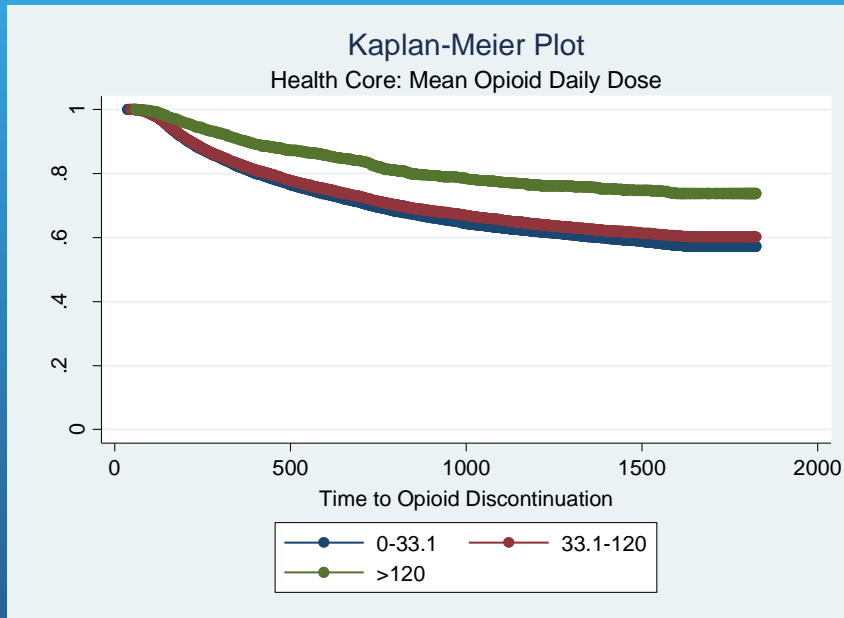
Source: CONSORT Survey (N=2119) Group Health Cooperative and Kaiser Permanente N CA

NOT ABLE TO COME OFF

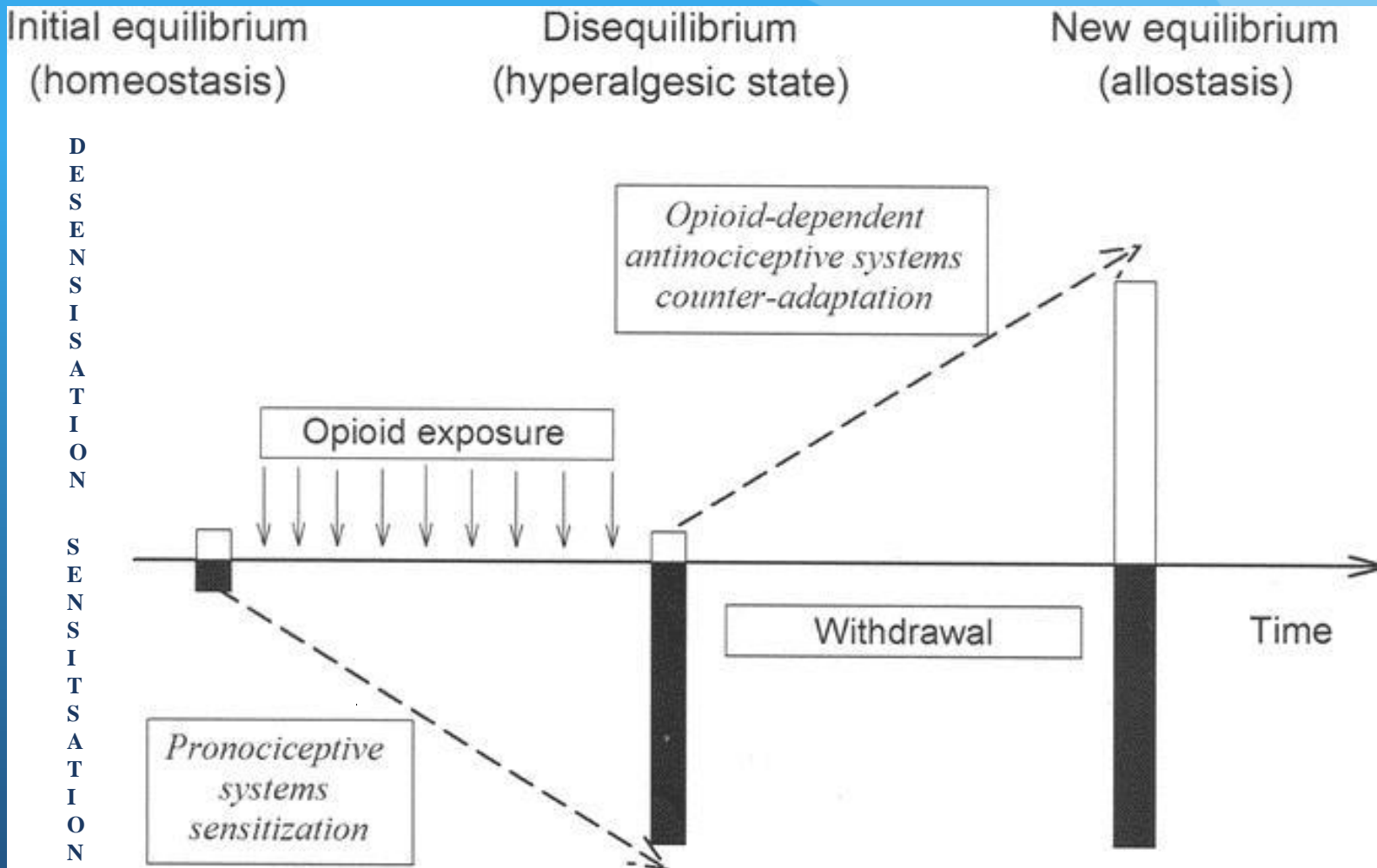
- Once started on a course of COT, how long do patients remain on opioids?
- TROUP study of COT recipients (used at least 90 days without a 32 day gap)
- Outcome: 6 months without any opioid Rx

Martin B, et al. , *J Gen Intern Med*, 2011; 26:1450-7.

COT discontinuation



Martin B, et al. , *J Gen Intern Med*, 2011; 26:1450-7.



Model of neuroadaptive changes underlying expression and recovery of opioid-induced hyperalgesia

Angst & Clark Anesthesiology 2006;104:570

Increase in neonatal abstinence

The JAMA Network

From: Neonatal Abstinence Syndrome and Associated Health Care Expenditures: United States, 2000-2009

JAMA. 2012;307(18):1934-1940. doi:10.1001/jama.2012.3951

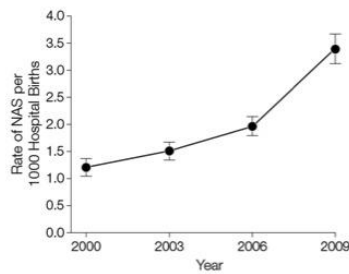


Figure Legend:

NAS indicates neonatal abstinence syndrome. Error bars indicate 95% CI. P for trend < .001 over the study period. The unweighted sample sizes for rates of NAS and for all other US hospital births are 2920 and 784 191 in 2000; 3761 and 890 582 in 2003; 5200 and 1 000 203 in 2006; and 9674 and 1 113 123 in 2009, respectively.

Date of download: 7/8/2012

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Increase in mothers on opioids

The JAMA Network

From: Neonatal Abstinence Syndrome and Associated Health Care Expenditures: United States, 2000-2009

JAMA. 2012;307(18):1934-1940. doi:10.1001/jama.2012.3951

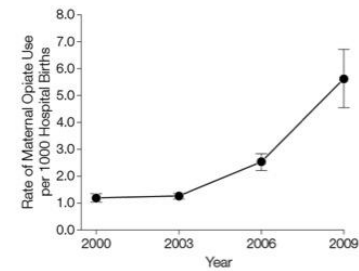


Figure Legend:

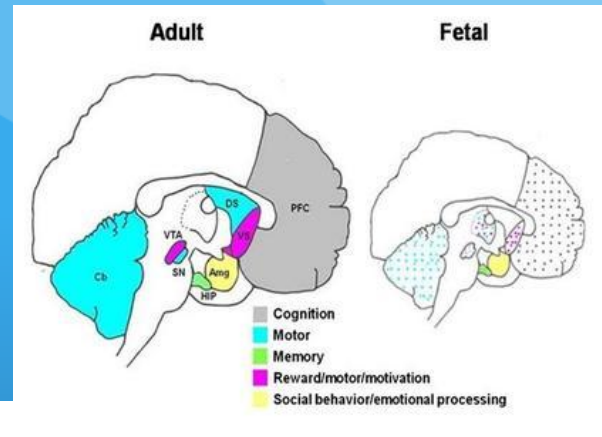
Error bars indicate 95% CI. P for trend < .001 over the study period. The unweighted sample sizes for mothers diagnosed with and without antepartum opiate use are 987 and 833 494 in 2000; 1058 and 849 133 in 2003; 2160 and 879 910 in 2006; and 4563 and 816 554 in 2009, respectively.

Date of download: 7/8/2012

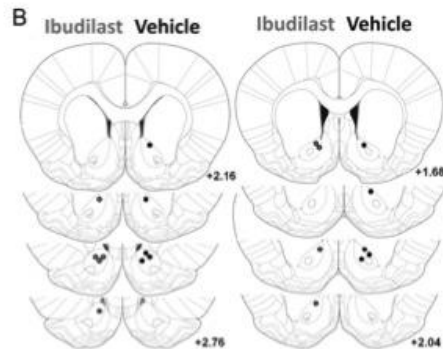
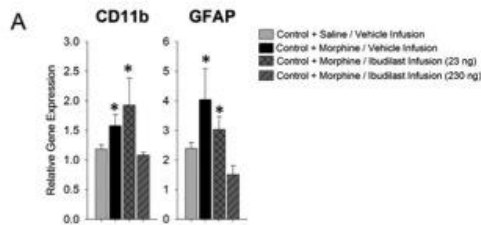
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The fetal brain is different

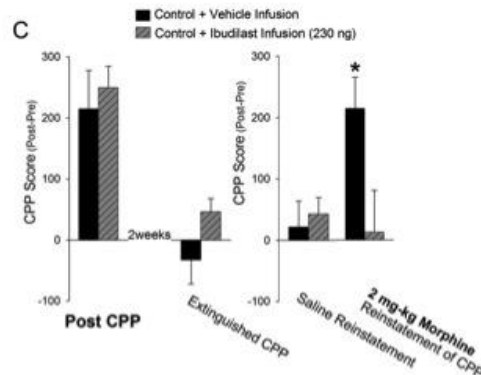
New studies suggest that fetal changes change abuse risk later in life



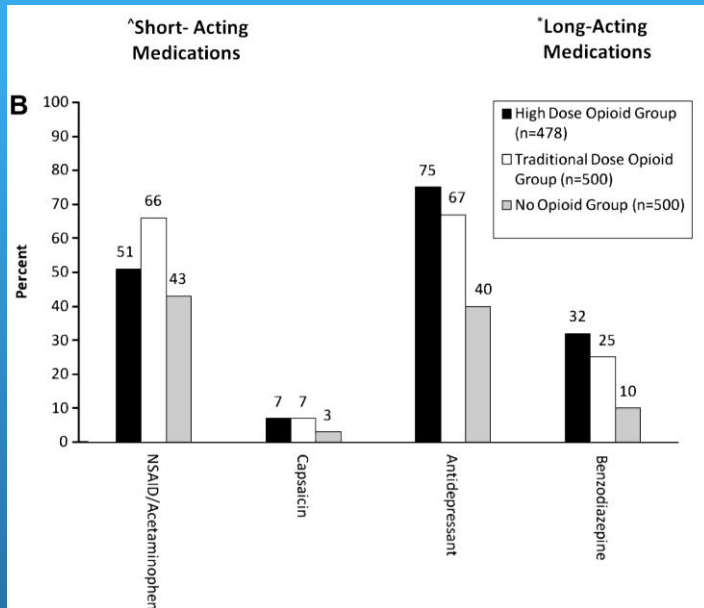
Infusion of ibudilast directly into the NAcc blocks the drug-induced reinstatement of morphine CPP in control rats.



Schwarz J M et al. J. Neurosci. 2011;31:17835-17847



ADVERSE SELECTION AND HIGH DOSE



Clinical characteristics of veterans prescribed high doses of opioid medications for chronic non-cancer pain

Morasco et al Pain 2010;151:625

Weisner et al Pain 2009;145:287-93

Morasco et al Pain 2010;151:625

Edlund et al Clin J Pain 2010;26:1-8

Martin et al J Gen Intern Med 2011;26:1450-7

Seal et al JAMA 2012;307:940-7

SUMMARY - Evidence from epidemiological studies, particularly high dose usage

Data from population studies have tended not to support good efficacy or safety

Cannot wean

- Significant problems with managing acute pain (surgical pain), as well as pain at the end of life
- Inability to wean during pregnancy a significant problem for neonates, possibly extending into adult life

Studies focused on return to work report opioid use delays return to work and impairs function

High association with mental health disorders, accounting in large part for high risk

Data on safety are showing concern of death, falls and fractures, endocrinopathies, particularly with high doses

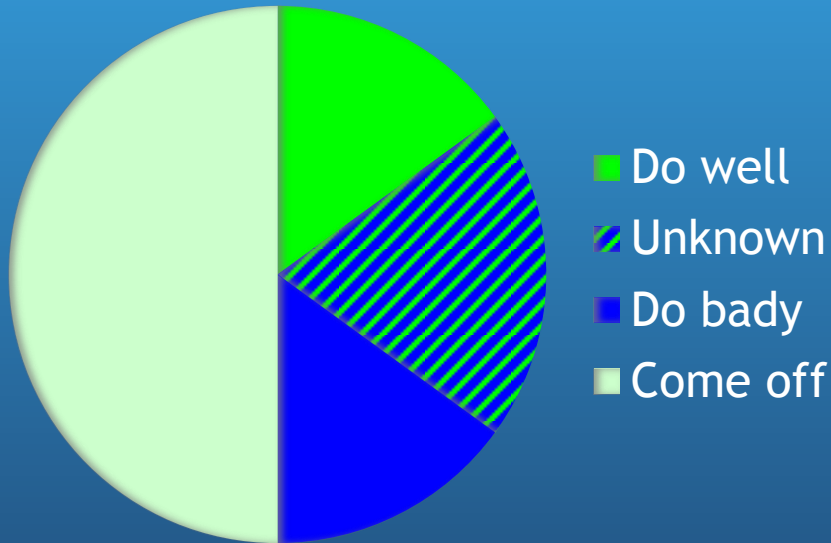
- Epidemiological data include all the patients who have dose escalated and are not doing well
- They include all the patients who are not treated in the careful practice settings that are typical of case series and open label follow up studies
- Since the 1980s, opioids are being used for an increasing 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

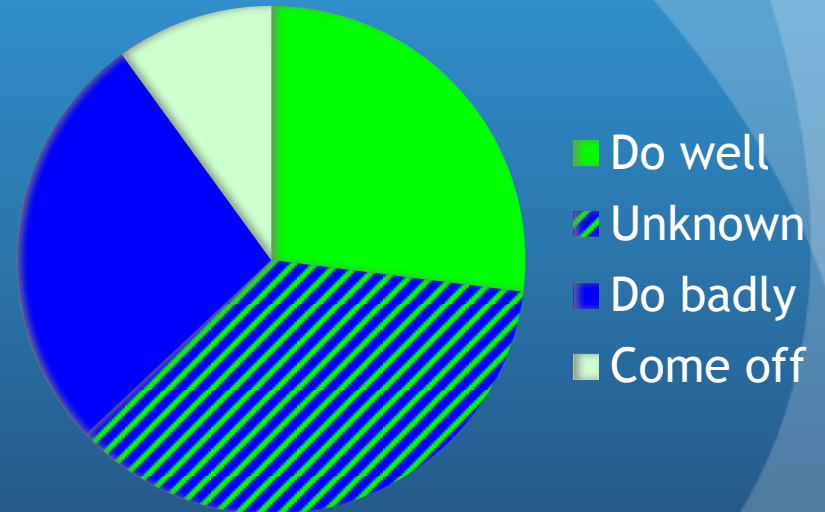
Sjorgen Epidemiology of chronic pain and critical issues on opioid use Pain 2011;6:1219-20

POPULATION DATA VERSUS TRIALS AND OBSERVATIONAL DATA

Cohort of patients who start on opioids



Population of patients at a given time point



RESEARCH GAPS

What characterizes the propensity to dose escalate:

- ◆ Patient
- ◆ Drug (long- vs short-acting, full vs partial agonists, weak vs strong)

How many stay on, don't escalate and do well?

Is there a cut-off dose in terms of safety?