

# WHAT IS THE EVIDENCE FOR THE EFFECTIVENESS OF OPIOID ANALGESICS FOR CHRONIC PAIN FROM CLINICAL AND ADMINISTRATIVE DATA

Jane C Ballantyne MD FRCA  
University of Washington School of Medicine  
Seattle, WA



# OBSERVATIONAL DATA

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

OBSERVATIONAL DATA

**EPIDEMIOLOGICAL DATA**

## Summary of epidemiological data

Large population studies have tended not to support good efficacy or function

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

Data on safety are showing concern of death, falls and fractures, related to high doses

Who dose escalates?

Who continues?

## 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

- 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

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:

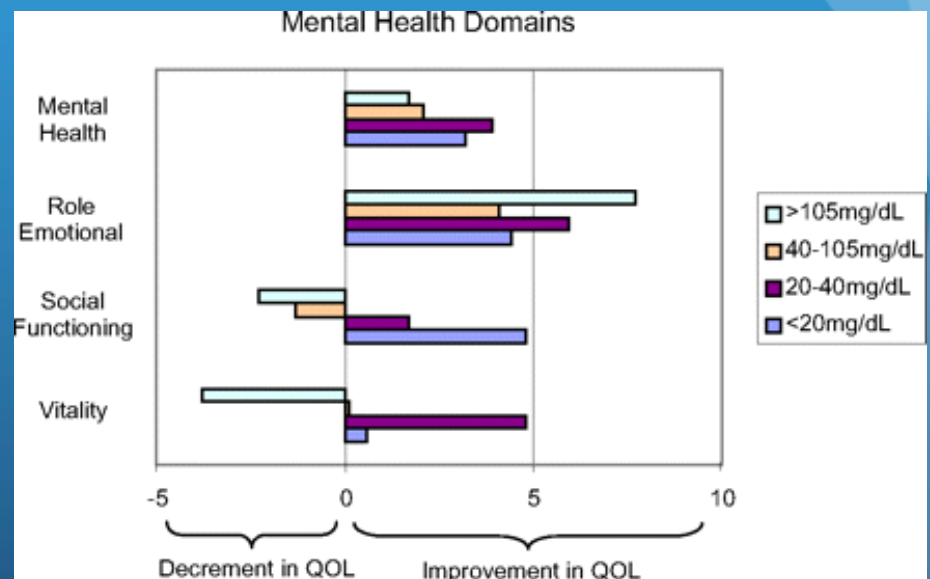
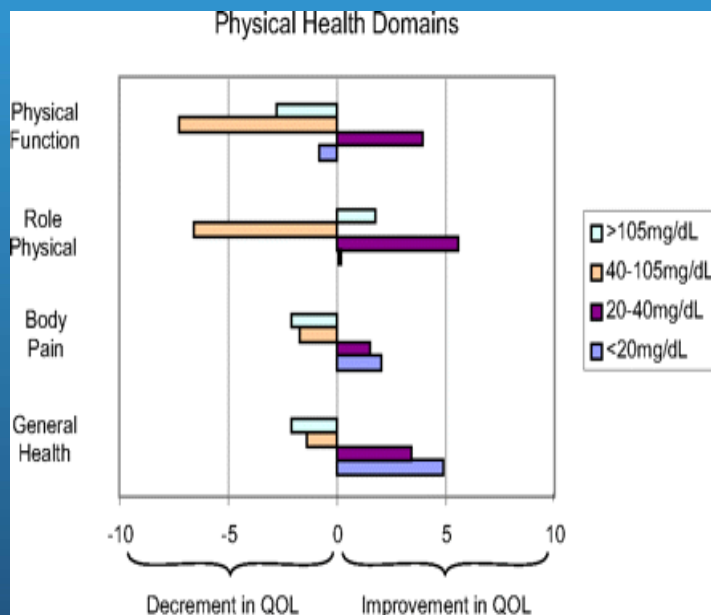
- reporting of severe pain
- poor self-rated health
- inactivity during leisure
- unemployment
- higher healthcare utilization
- poor health orientated quality of life on SF-36

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



# 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

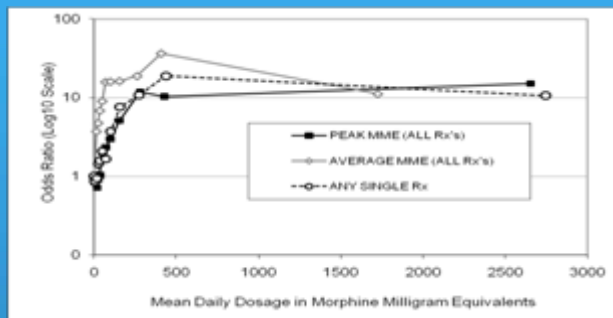
Webster et al Spine 2007;32:2127-32

Franklin et al Spine 2008;33:199-204

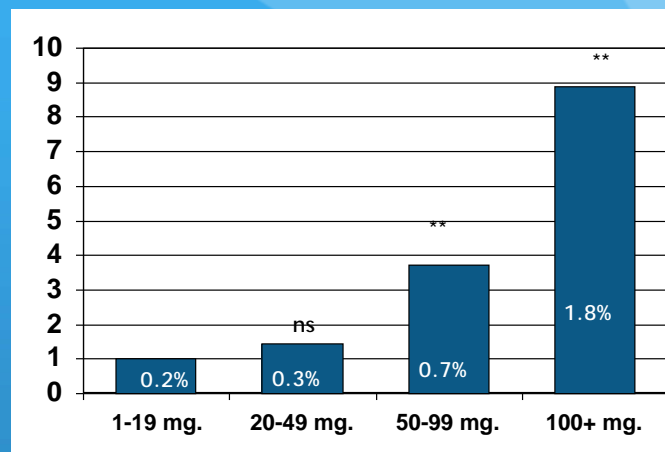
Gross et al Spine 2009;35:525-31

Volinn et al Pain 2009;142:194-201

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

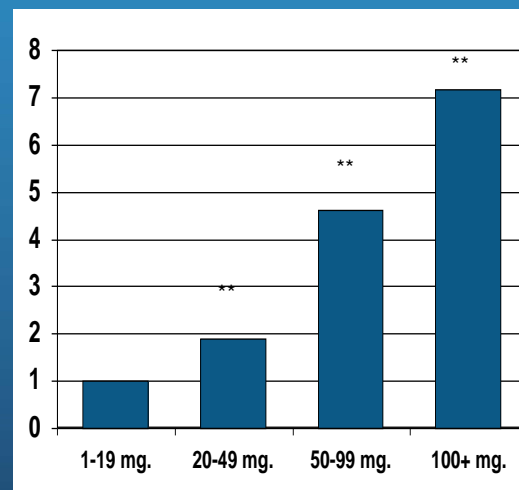
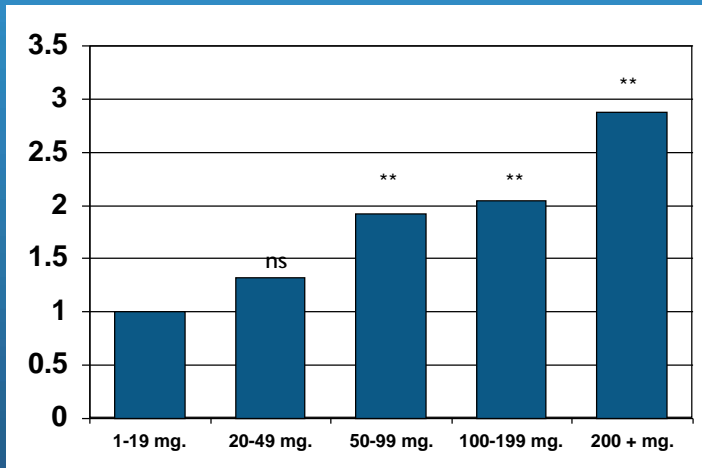


# DEATHS AND HIGH DOSES



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

# WHO DOSE ESCALATES?

**Portenoy et al 2007** registry study for 3 yrs  
39/219 reached 3 yrs, 44% needed dose increase by month 3, 23% months 4-6 and 17% months 10-12, 8-13% each time interval after

**Schneider & Kirsch 2010** chart review to 56 months  
40% reached stable dose (mean 180 MED), 22% escalated but then stabilized, 38% never stabilized

**Naliboff et al 2011** RCT escalate vs no escalation for 12 months  
80% vs 16%; short term benefit in escalating group, but did not last; no group differences in usual pain or function

**Martin et al 2011** claims data up to 2.3 yrs  
2/3 receiving >90 days remain on years later, associated strongly with >120 MG, misuse, intermittent prior exposure

Portenoy et al Clin J Pain 2007;23:287-99

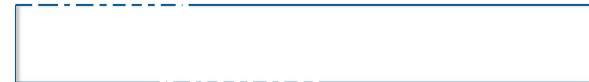
Schneider & Kirsch J Opioid Manag 2010;6:385

Naliboff et al J Pain 2011;12:288-96

Martin et al J Gen Intern Med 2011;26:1450-57

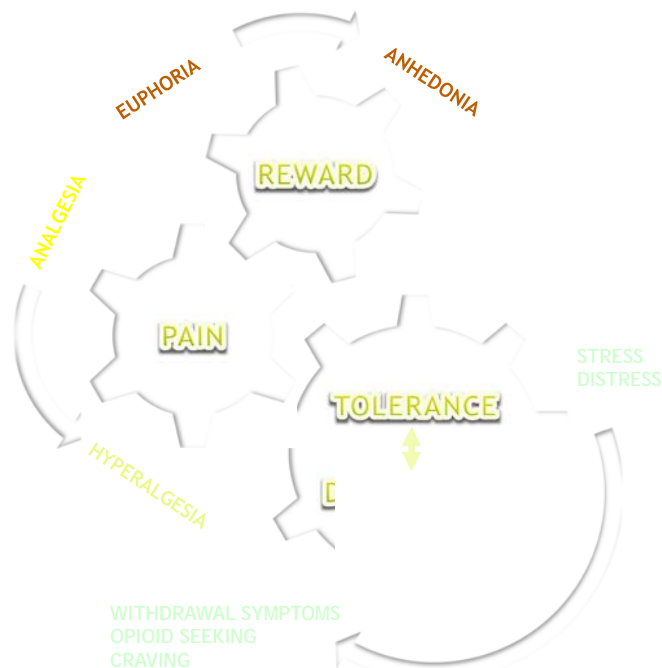
Tolerance is closely linked to dependence and is a one way passage to higher doses

## Natural History of Opioid Dependence



- Dependence makes it hard to come off opioids even in the face of poor effect
- People in withdrawal experience worse pain
- Makes study design difficult because efficacy depends more on whether on the way up or down, than on dose

Tompkins & Campbell Curr Pain Headache Rep  
2011;15:129-136  
Pud et al Drug Alcohol Depend 2006;82:218-233



# PAIN AND FUNCTION OFTEN IMPROVE FOR PATIENTS WHO SUCCESSFULLY TAPER OFF OPIOIDS

**Brodner & Taub** Mt Sinai J Med 1978;45:233-237

**Taylor et al** Pain 1980;8:319-329

**Finlayson et al** Pain 1986;26:167-174 & 175-18

**Ralphs et al** Pain 1994;56:279-288

**Jensen et al** J Consult Clin Psychol 2001;69:655-662

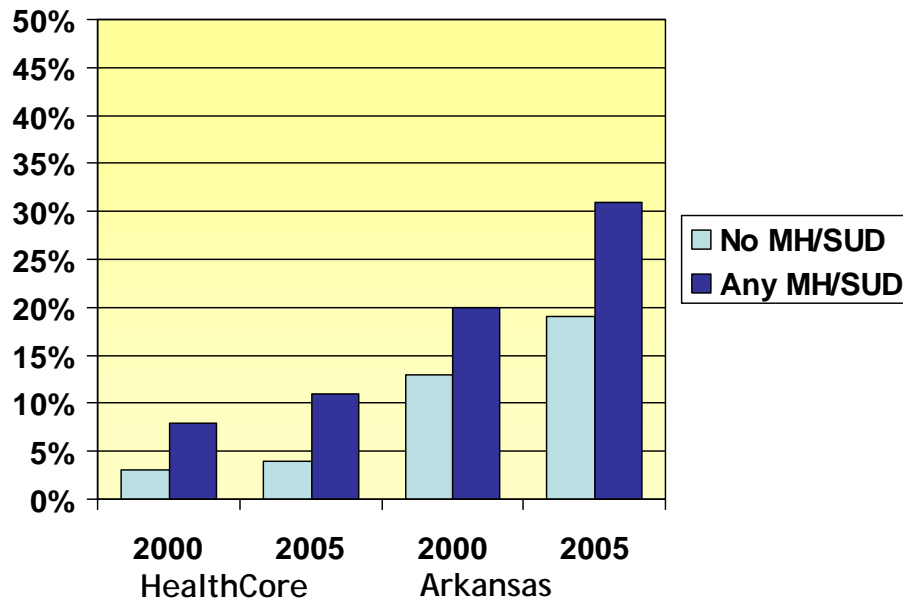
**Baron & McDonald** J Opioid Manag 2006;2:277-282

**Hooten et al** Pain Med 2007;8:8-16

**Townsend et al** Pain 2008;140:177-189

**Kidner et al** J Bone Joint Surg Am 2009;91:919-927

# 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;307:940-7

## SUMMARY – OBSERVATIONAL DATA

- 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

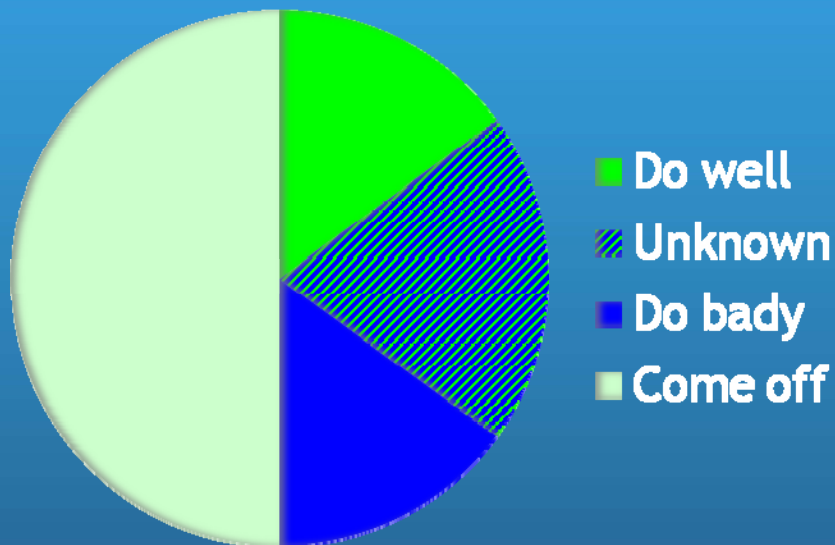
## SUMMARY - EPIDEMIOLOGICAL DATA

- 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)

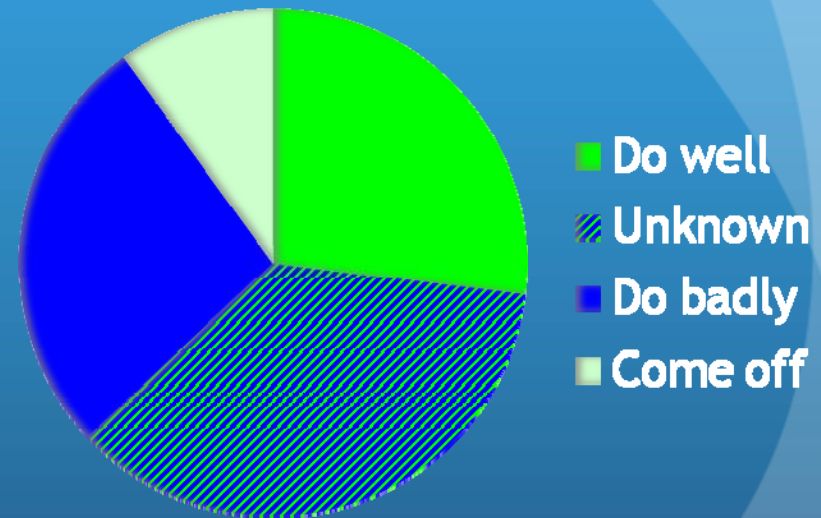


# POPULATION VERSUS OBSERVATIONAL DATA

**Cohort of patients who start on opioids**



**Population of patients at a given time point**



## 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

## 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?