Buprenorphine Use in Combined Chronic Pain and Opioid Addiction

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Disclosures

- Within the last 3 years, consulted for AstraZeneca, BioDelivery Sciences, Camarus, Clinilabs, Grunenthal, Guidepoint Global, Janssen, Mallinckrodt, Pfizer, Salix, Shire
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The Problem

- Opioid prescribing, abuse, and overdose have increased substantially in the past decade

The Problem

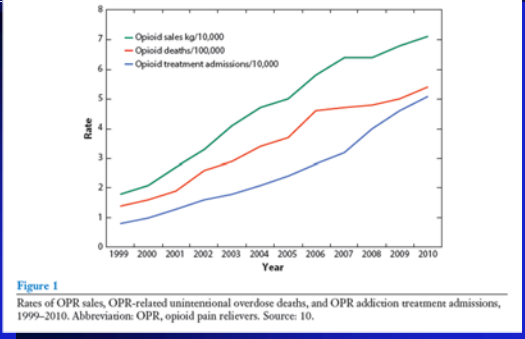


Figure 1
Rates of OPR sales, OPR-related unintentional overdose deaths, and OPR addiction treatment admissions, 1999–2010. Abbreviation: OPR, opioid pain relievers. Source: 10.

Kolodny et al. 2015 (figure from MMWR 60: 1487-92, 2011)

The Problem

- Opioid prescribing, abuse, and overdose have increased substantially in the past decade
- Among patients with pain, some estimates suggest that opioid abuse is prevalent

The Problem

- The prevalence of opioid abuse in chronic pain patients is 20-24% across healthcare settings (Sullivan et al., 2010)
- Of 705 patients receiving chronic opioid therapy for pain, 26% reported a current opioid use disorder and 36% had lifetime OUD (Boscarino et al., 2010)

The Problem

- Opioid prescribing, abuse, and overdose have increased substantially in the past decade
- Among patients with pain, some estimates suggest that opioid abuse is prevalent
- Relationship between pain and abuse of opioids is not well understood and the most effective way of treating these co-occurring disorders is not clear

Primary Goals

1. How to identify the patient population
2. Discuss the rationale and evidence supporting the use of SL buprenorphine/naloxone to treat co-occurring pain and opioid use disorder
3. Briefly summarize what we do and don't know about this treatment approach

Primary Goals

1. How to identify the patient population

Behaviors of Patients with Chronic Pain and Opioid Use Disorder

- Sell or forge prescriptions
- Alter route of administration
- Obtain prescriptions from non-medical sources
- "Doctor shop"
- Escalate dose or fail to comply with regimen
- "Lose" medication
- Deteriorate in function

Portenoy & Payne, 1997

Screening Instruments for Opioid Abuse Risk

Prescription Drug Use Questionnaire (PDUQ) *(Compton et al. 1998)* Hoarding pills; using analgesics to relieve symptoms other than pain; supplementing with alcohol or drugs

Pain Assessment and Documentation Tool (PADT) *(Passik et al. 2004)* 4 domains: (1) pain relief, (2) patient functioning, (3) adverse events, (4) drug-related behaviors

Screener and Opioid Assessment for Patients with Pain (SOAPP) *(Butler et al. 2009)* High vs low risk of aberrant medication-related behaviors based on substance use, legal problems, craving, heavy smoking , mood swings

Risk Assessment for Patients on Opioid Therapy for Pain

Low-risk patients:
- No history of substance abuse
- Lack any major psychiatric co-morbidity
- No indication of aberrant behaviors
- Can be managed in primary care setting

Medium risk:
- Prior history or family history of substance abuse
- May have psychiatric co-morbidity
- Can be managed in primary care with consultation from specialist

High risk:
- Active addictive disorders
- At increased risk for aberrant behaviors
- Should be referred to a pain management clinic

Gourlay DL et al. Pain Med 2005; 6(2): 107-12.

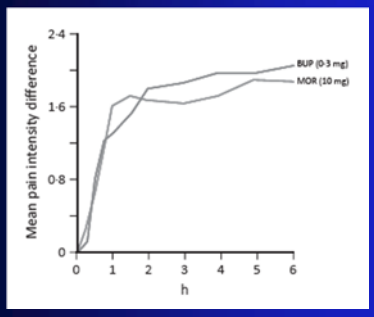
Primary Goals

1. How to identify the patient population
2. Discuss the rationale and evidence supporting the use of SL buprenorphine/naloxone to treat co-occurring pain and opioid use disorder

Why Buprenorphine?

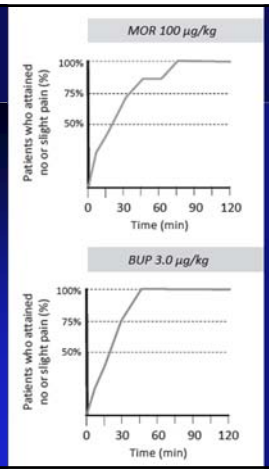
1. It has been marketed in parenteral form as an analgesic since 1985
2. When given parenterally, it produces analgesia that is comparable to morphine and other “strong” analgesics

IM Bup vs IM Mor for Post-op Pain in Adults (Upper Abdominal; N=60)



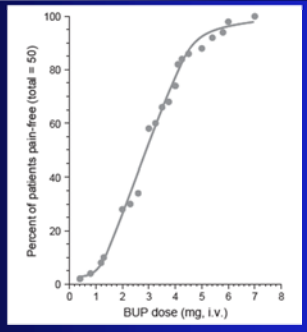
Reviewed in Raffa et al., 2014

IV Bup vs IV Mor for Post-op Pain in Children (Lateral Thoracotomy; N=57)



Reviewed in Raffa et al., 2014

IV Bup for Post-operative Pain in Women (C-section; N=50)



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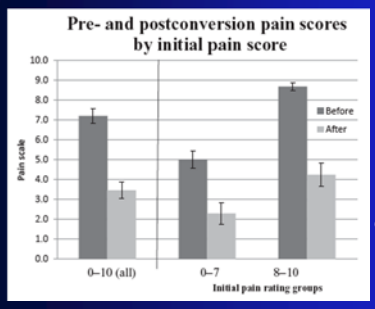
Why Buprenorphine?

1. It has been marketed in parenteral form as an analgesic since 1985
2. When given parenterally, it produces analgesia that is comparable to morphine and other “strong” analgesics
3. Sublingual/buccal formulations of buprenorphine are currently approved for treating opioid dependence
4. SL buprenorphine is safe, well-tolerated, and effective in treating OUD
5. Is SL buprenorphine effective in treating chronic pain?

SL Bup for Patients with Chronic Pain (mean daily MED=550 mg; N=35)



Average dose of SL bup = 28.11 ± 5.94 mg*

****Patients instructed not to exceed 32 mg/day***

Daitch et al., 2014

Why Buprenorphine?

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4. SL buprenorphine is safe, well-tolerated, and effective in treating OUD
5. Is SL buprenorphine effective in treating chronic pain?
6. **What about treating patients with co-occurring pain and abuse?**

Buprenorphine/naloxone for Treatment of Chronic Pain and Prescription Opioid Abuse

PI: Maria A. Sullivan, MD, PhD

Participants

- Inclusion criteria: maintained on prescription opioids for chronic pain condition of moderate severity (4-7 out of 10)
- Exclusion criteria: regular use of methadone (>30 mg/wk), history of opioid overdose in past 3 years, unstable medical condition, severe mood disorder or psychosis, physiological dependence on alcohol or sedative-hypnotics.

Study Design

- 2-phase study included 7-week inpatient followed by a 12-week outpatient phase
- Bup/Nx administered on a QID dosing schedule

Study Design: Outpatient Phase

End of inpatient phase: Discharged on 16 mg Bup/Nx ± 25% standing dose for PRN (MDD=32 mg)

Twice-weekly assessments throughout the 12-week outpatient phase:

- Urine samples for drug toxicology
- Subjective reports of clinical pain
- Adverse events

Participant Demographics

Characteristics	(n=51)
Age (years)	47.4 ± 9.4
Male	68.6%
Race/Ethnicity	
Caucasian	47.1%
African-American	29.4%
Hispanic	23.5%
Currently married	28.6%
Education (years)	13.3 ± 2.1

Pattern of Opioid Use

Duration of use (years)	6.1 ± 10.8
Heroin use	
Current	13.7%
Past only	11.8%
History of altering oral route of opioid use (IN or chewed)	11.1%
Morphine equivalence (mg/day)	183.1 ± 247.0
Methadone	
Reported current illicit use	7.8%
U-tox at screening	15.7%

Other Drugs of Abuse

Cocaine	
Days used in last 7 days	1.1 ± 2.3
U-tox at screening	23.5%
Marijuana	
Days used in last 7 days	0.2 ± 1.3
U-tox at screening	11.8%
Alcohol	
Days used in last 7 days	0.8 ± 1.4
Current alcohol abuse	6.0%
Past-only alcohol abuse/dependence	24.0%

Pain Demographics

Type of pain	
Lower back pain	58.8% (n=30)
Arthritis (osteoarthritis, rheumatoid)	17.6% (n=9)
Other musculoskeletal	43.1% (n=22)
Other (i.e. neuropathy, Lyme's disease, fibromyalgia)	19.6% (n=10)
Mean duration of pain (years)	8.4 ± 9.6
Number of pain syndrome categories reported	
One only	62.7% (n=32)
Two only	35.3% (n=10)
Three or more	2.0% (n=1)

Pain Ratings on PADT

	Baseline	Outpt Week 1	Outpt Week 4	Outpt Week 8	Outpt Week 12
	n=45	n=29	n=23	n=20	n=18
*Mean pain during previous week**	6.0 (1.3)	4.1 (2.6)	4.2 (2.5)	4.2 (2.4)	3.9 (2.5)
*Mean worst pain during previous week**	8.7 (1.1)	6.2 (3.1)	6.5 (2.9)	5.8 (3.1)	5.4 (3.0)
Mean percentage of pain relieved by current medication	55.6 (27.8)	69.4 (25.9)	68.9 (21.3)	67.4 (26.8)	74 (19.7)
Pain relief enough to make a difference (patient rating)	81.8%	96.7%	90.9%	94.7%	100%

*Rating from 0 (No pain) to 10 (Pain as bad as it can be)

Potential Aberrant Behaviors on PADT

	Baseline	Outpt Weeks 1-12
	n=45	n=29
Purposeful oversedation	28.3%	10.3%
Requests frequent early renewals	52.2%	3.4%
Increases dose without authorization	89.1%	13.8%
Reports lost or stolen prescriptions	13.0%	3.4%
Changes route of administration	10.9%	0.0%
Uses pain medication in response to situational stressor	43.5%	13.8%

Urine Drug Toxicology

	Week 1	Week 4	Week 8	Week 12
	n=29	n=23	n=20	n=18
% Opioid Abstinent	88.5%	90.0%	95.0%	93.4%

Adverse Events

	Week 1	Week 4	Week 8	Week 12
	n=29	n=23	n=20	n=18
Nausea	23.3%	8.7%	15.0%	5.6%
Vomiting	6.7%	8.7%	5.0%	0.0%
Constipation	73.3%	60.9%	50.0%	66.7%
Itching	3.3%	0.0%	5.0%	5.6%
Mental cloudiness	3.3%	0.0%	5.0%	0.0%
Sweating	20.0%	17.4%	20.0%	11.1%
Fatigue	23.3%	13.0%	20.0%	11.1%
Drowsiness	26.7%	13.0%	20.0%	5.6%

Conclusion

- SL Bup/Nx was well tolerated and effective in treating both pain and opioid abuse

Unanswered Questions

- Does pain modulate the effects of opioids in patients with OUD?
- What is the optimal dose of SL Bup for treating pain and/or opioid abuse?

Patients with Opioid Abuse: Comparison of Those With and Without Chronic Pain

Study Design: Inpatient Setting

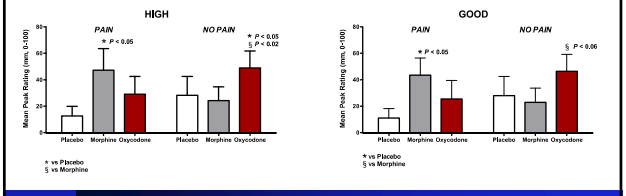
Week	Mon	Tue	Wed	Thu	Fri
1	Stabilize on SL buprenorphine (4 mg BID)				
2			Cum Mor (Safety)		Cum Oxy (Safety)
3	Sample A (Placebo)		Sample B (120 mg Oxy)		Sample C (360 mg Mor)
4	Choice (A, B, or C)	Choice (A, B, or C)	Choice (A, B, or C)	Choice (A, B, or C)	Choice (A, B, or C)

Outcome Measures

- Subjective effects (e.g., "I feel a good effect")
- Physiological effects (miosis, respiration, etc.)
- Drug self administration

Measure	With Pain (N=7)	Without Pain (N=9)
Age (yrs)	44 ± 4	44 ± 3
Sex	6M/1F	8M/1F
Ethnicity	3B/1W/3H	5B/1W/2H/1Mixed
Opioid Use	Heroin (N=3), RxOp (N=2), Heroin + RxOp (N=2)	Heroin (N=3), RxOp (N=2), Heroin + RxOp (N=4)
Alcohol Use	1x/week or less (N=3)	1-3x/week or less (N=6)
Cigarette Use	5-20/day (N=6)	5-20/day (N=8)
MJ Use	3x/month (N=1)	2x/week or less (N=3)
Cocaine Use	1-2x/week or less (N=3)	1-3x/week or less (N=6)
Types of Pain	Lower back (7)	None
Pain During Screening	5.9 ± 0.9	1.0 ± 0.4
Pain During Study	3.1 ± 0.8	0.6 ± 0.3

SUBJECTIVE EFFECTS



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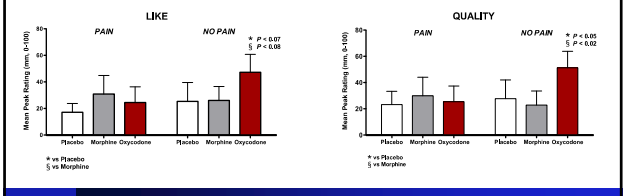
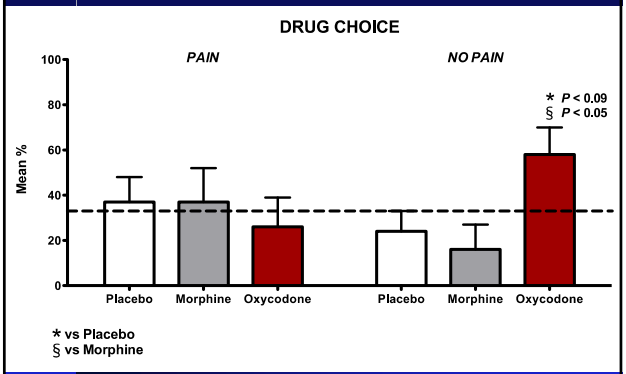


DRUG SELF-ADMINISTRATION



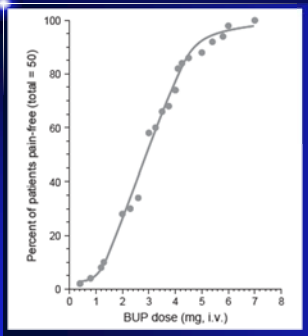
Conclusions

- Participants with pain can discriminate the effects of morphine and placebo ("High" and "Good Effects"), but they don't like it and don't self-administer it above placebo levels
- Participants without pain can discriminate the effects of oxycodone and placebo ("High," "Good Effects," "Like," "Quality") and they self-administer it
- Pain appears to modulate the subjective and reinforcing effects of opioids in opioid abusers

Unanswered Questions

- Does pain modulate the effects of opioids in patients with OUD?
- What is the optimal dose of SL Bup for treating pain and/or opioid abuse?

Is There a "Ceiling" on Bup-induced Analgesia?



IV Bup for Post-op Pain in Women (C-section; N=50)

Reviewed in Raffa et al., 2014

Is There a "Ceiling" on Bup for Treating OUD?

Review

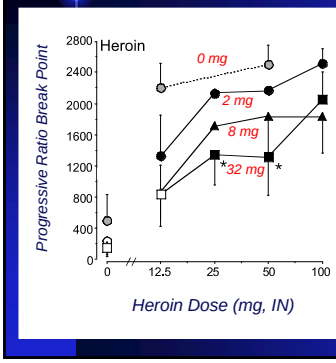
Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: Implications for clinical use and policy

Mark K. Greenwald[a,*], Sandra D. Comer[b], David A. Fiellin[c]

Summary:

- The number of receptors that need to be occupied by buprenorphine to reverse opioid withdrawal is ~50% (~4 mg or lower divided doses)
- The number of receptors that need to be occupied by buprenorphine to block opioid agonist effects is ~80% (~16 mg or lower divided doses)
- Even more receptors need to be occupied by buprenorphine to block high doses of opioids (90%+)

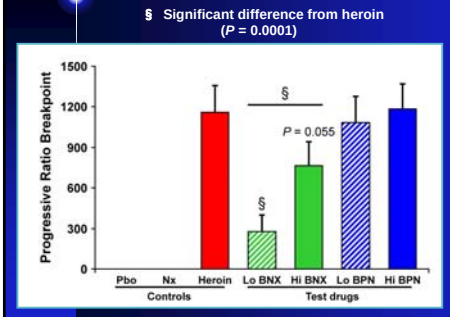
Buprenorphine/Naloxone Maintenance and IN Heroin Self-administration



- Ss maintained on SL Bup/Nx (0, 2, 8, 32 mg)
- Testing w heroin occurred at trough Bup/Nx levels (~15 hrs after dosing)
- Bottom line: Even on 32 mg maintenance, heroin is still self-administered

Comer et al., 2005

BUT, caution…Bup and Bup/Nx are abused



- Ss maintained on SL Bup (2, 8, 24 mg)
- Testing occurred at trough Bup levels (~15 hrs after dosing)
- Bottom line: Benefit of higher Bup doses must be weighed against risk of abuse

Comer et al., 2010

Overall Conclusions

- SL Bup/Nx was well tolerated and effective in treating both pain and opioid abuse
- Areas for further research:
  - Is there a ceiling on bup-induced analgesia?
  - Should there be a cap on bup for OUD?

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