Risk Assessments Used When Studying Traditional Mu Agents

Kenzie L. Preston, Ph.D.

NIDA Intramural Research Program

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ACTTION: Outcomes for Assessing Treatment for Opioid Use Disorder

Risk Assessment

Adverse Events

Dependence Potential

Opioid Antagonist Activity

Physical Dependence Potential

Risk Assessment

Adverse Events

Do undesired/harmful/unintended effects result from taking the medication

Dependence Potential

Opioid Antagonist Activity

Physical Dependence Potential

Mu Agonist Actions

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Anesthesiology. 2011 December ; 115(6): 1363–1381. doi:10.1097/ALN.0b013e318238bba6.

Molecular Mechanisms of Opioid Receptor-Dependent Signaling and Behavior

Ream Al-Hasani, Ph.D* and Michael R. Bruchas, Ph.D†

Table 1

Organ system effects of morphine and its surrogates. The actions summarized in this table are observed for all clinically available opioid agonists

Organ Systems	Effects
Central Nervous system	↑ Analgesia
	↑ Euphoria
	↑Sedation
	↓ Rate of respiration
	↓ Cough reflex
	↑ Miosis-Constriction of the pupils
	↑ Truncal rigidity
	↑ Nausea and vomiting
Peripheral	**Gastrointestinal system**
	↑ Constipation
	↓ Gastric motility
	↓ Digestion in the small intestine
	↓ Peristaltic waves in the colon
	↑ Constriction of biliary smooth muscle
	↑ Esophageal reflux
	Other smooth muscle
	↑ Depression of renal function
	↓ Uterine tone
	↑ Urinary retention
	Skin
	↑ Itching and sweating
	↑ Flushing of the face, neck and thorax
	Cardiovascular system
	↓ Blood pressure and heart rate if cardiovascular system is stressed
	Immune System
	↓ Formation of rosettes by human lymphocytes
	↓ Cytotoxic activity of natural killer cells
	Other
	Behavioral restlessness

Adverse Events – Mu Agonists

Serious: respiratory depression
apnea
circulatory depression
respiratory arrest
shock
cardiac arrest
anaphylactoid reactions (rare)

Most frequent: constipation
nausea
somnolence

Commonly observed:
lightheadedness, dizziness
sedation, vomiting, sweating

Other less frequent:
Body as a Whole: malaise, withdrawal syndrome
Cardiovascular : bradycardia, hypertension, hypotension, palpitations, syncope, tachycardia
Digestive: biliary pain, dyspepsia, dysphagia, gastroenteritis, abnormal liver function tests, rectal disorder, thirst
Endocrine: hypogonadism
Hemic and Lymphatic: anemia, thrombocytopenia
Metabolic and Nutritional: edema, weight loss
Musculoskeletal: skeletal muscle rigidity
Nervous System: abnormal dreams, abnormal gait, agitation, amnesia, anxiety, ataxia, confusion, convulsions, coma, delirium, hallucinations, lethargy, nervousness, abnormal thinking, tremor, vasodilation, vertigo, headache
Respiratory: hiccup, hypoventilation, voice alteration
Skin and Appendages: dry skin, urticaria, pruritus
Special Senses: amblyopia, eye pain, taste perversion
Urogenital: abnormal ejaculation, dysuria, impotence, decreased libido, oliguria, urinary retention, anti-diuretic effect
Serotonin syndrome: during concomitant use of opioids with serotonergic drugs.
Adrenal insufficiency: with opioid use, more often following greater than one month of use.
Androgen deficiency: with chronic use of opioids.

Not all Mu agonists have the same adverse effects

Off target effects

Methadone – QTc prolongation (blocks flow of potassium ions through HERG channels)
Torsades de pointes

Molecule specific

metabolism, allergy

Codeine

interactions with drugs affecting Cytochrome P450 isoenzymes
allergy

Meperidine

metabolite with serotonin effects – serotonin syndrome;

Safety Assessment

Treatment-emergent adverse events

Clinical laboratory parameters

Vital signs

Physiological parameters

Electrocardiograms

Adverse Event Assessment
Spontaneous Reports

Research staff asking participants
"How have you been feeling since the last visit?"
May ask about specific events, depends on a particular study's safety concerns.

Spontaneously reported events recorded at any visit.

Specific recording and reporting procedures.

All AEs and SAEs are managed, reported, and followed according to applicable regulatory requirements.

Source: Udi Ghitza, Ph.D. NIDA CCTN

General Inquiry

Have you had any physical or health problems since your last visit?

Have you noticed any changes in your physical appearance since your last visit?

Have you cut down on the things you usually do because you have not felt well physically since your last visit?

Specific Events

Have you had any of the following problems since your last visit?

Modified SAFTEE (version used in COMBINE study)

Center | Patient # | Patient Initials | Week | Sequence | Date (month / day / year) | Staff ID #

Instructions: Complete at all visits for patients who are assigned to MM. For further instructions, see ***SAFTEE Guidelines*** **Parts 1** and **2** (Forms A–8 and A–9).

Question	Event	Date of Onset	Duration (Days)	Pattern	Severity	Drug Related	Action Taken
				IS IN CO	MN MI MO S	N DR TO K O X	N IS C SU DC O R I
A. General Inquiry Have you had any physical or health problems since your last visit? Have you noticed any changes in your physical appearance since your last visit? Have you cut down on the things you usually do because you have not felt well physically since your last visit?	1 2 3 4 5 6 7 8 9 10						
				IS=Isolated IN=Intermittent CO=Continuous	MN=Minimal MI=Mild MO=Moderate S=Severe	N=No DR=Dose-response TO=Timing of onset K=Known drug effect O=Other (specify) X=Don't know	N=None IS=Increased surveillance C=Centre active RX SU=Suspend RX DC=Discontinue RX O=Other R=Dose reduction I=Dose increased

Question	Event	Date of Onset	Duration (Days)	Pattern	Severity	Drug Related	Action Taken
	Prev /Rec Y N			IS IN CO	MN MI MO S	N DR TO K O X	N IS C SU DC O R I
B. Specific Events Have you had any of the following problems since your last visit? 1. Nausea 2. Vomiting 3. Diarrhea 4. Abdominal pain 5. Decreased appetite 6. Increased appetite 7. Headache 8. Dizziness 9. Fatigue 10. Nervousness/anxiety 11. Insomnia 12. Somnolence 13. Depression* 14. Itching 15. Rash 16. Decreased libido 17. Increased libido 18. Mood swings 19. Significant lab abnormalities (describe) 20. Other (describe) 21. Other (describe)							
* Requires additional specification				IS=Isolated IN=Intermittent CO=Continuous	MN=Minimal MI=Mild MO=Moderate S=Severe	N=No DR=Dose-response TO=Timing of onset K=Known drug effect O=Other (specify) X=Don't know	N=None IS=Increased surveillance C=Centre active RX SU=Suspend RX DC=Discontinue RX O=Other R=Dose reduction I=Dose increased

Standardized Severity Indicators

Common Symptom Severity Indicators

Severity:	*Minimal*	*Mild*	*Moderate*	*Severe*

1. **Nausea**

   Minimal Single occurrence lasting less than 2 hours; no change in eating habits
   Mild Multiple occurrences or duration of longer than 2 hours; no change in eating habits
   Moderate Intake significantly less than minimum daily requirement, but able to eat
   Severe No significant nutritional intake

2. **Vomiting**

   Minimal Stomach contractions, retching, or heartburn without emesis
   Mild One episode in any 24-hour period
   Moderate Two to 5 episodes in 24 hours, or 1 episode per day on 5 days or less
   Severe Six to 10 episodes in 24 hours, or more than 1 episode on more than 5 days

3. **Diarrhea**

   Minimal Loose but not watery stools, without cramping or incontinence
   Mild Diarrhea without cramping or incontinence, or 2 or fewer episodes per day
   Moderate Diarrhea with cramping, no incontinence, or 3 or more episodes per day
   Severe Diarrhea with incontinence and cramping, or 6 or more episodes per day

4. **Abdominal Pain**

   Minimal Single occurrence of abdominal pain that is not distressing and does not limit activities
   Mild Multiple occurrences of abdominal pain that are not distressing and do not limit activities
   Moderate Single or multiple occurrences of abdominal pain that cause distress but do not limit activities
   Severe Abdominal pain or cramping of sufficient severity to limit activities

Risk Assessment

Adverse Events

Dependence Potential

Opioid Antagonist Activity

Physical Dependence Potential

Tramadol

Marketed analgesic

Examined for potential utility in treatment of opioid use disorder

Traditional/nontraditional Mu agent

Mu agonist activity plus noradrenergic and serotonergic reuptake blockade

Has been tested in the wide range of risk assessments

Risk Assessment

Adverse Events

Dependence Potential

How likely that this medication will be abused, diverted, or lead to addiction

Opioid Antagonist Activity

Physical Dependence Potential

Dependence Potential

"Single dose studies"

Self-administration

Drug Discrimination

"Single Dose"/Acute Drug Administration Studies

Determine the profile of effects of the test drug

Subjective, Physiological, Pharmacokinetic

Compared to placebo and a prototypic drug

i.e., a drug with significant abuse

Dose response curve - 2 or more doses of each drug tested

Higher than therapeutic doses

Double blind

Random assignment and/or crossover design

Study population – individuals with experience using drugs within the same class

Typical Subjective Effect Measures Used in Abuse Liability Testing

Positive Mood Effects

Global Effects

Examples: Drug Effect, Liking, High, Good Effects, Bad Effects

Addiction Research Center Inventory (ARCI)

Many subscales, examples:

Morphine-Benzedrine Group (MBG) - euphoria

Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) - sedation

LSD - dysphoria, apathetic sedation, somatic discomfort

Symptom Questionnaire

Examples: Nodding, Drunk, Nausea

Drug Class Questionnaire (Type of Drug)

Examples: opiate, benzodiazepine, alcohol

Typical Subjective Effect Measures Used in Abuse Liability Testing

Negative Mood Effects

Global Effects

Examples: Drug Effect, Liking, High, Good Effects, Bad Effects

Addiction Research Center Inventory (ARCI)

Many subscales, examples:

Morphine-Benzedrine Group (MBG) - euphoria

Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) - sedation

LSD - dysphoria, apathetic sedation, somatic discomfort

Symptom Questionnaire

Examples: Nodding, Drunk, Nausea

Drug Class Questionnaire (Type of Drug)

Examples: opiate, benzodiazepine, alcohol

Typical Subjective Effect Measures Used in Abuse Liability Testing

Qualitative Description of Effects

Global Effects

Examples: Drug Effect, Liking, High, Good Effects, Bad Effects

Addiction Research Center Inventory (ARCI)

Many subscales, examples:

Morphine-Benzedrine Group (MBG) - euphoria

Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) - sedation

LSD - dysphoria, apathetic sedation, somatic discomfort

Symptom Questionnaire

Examples: Nodding, Drunk, Nausea

Drug Class Questionnaire (Type of Drug)

Examples: opiate, benzodiazepine, alcohol

Measuring "Euphoria"

- Liking - How much do you like the drug?
  - Lickert scales
  - Visual analog scales

- Morphine-Benzedrine Group (MBG) scale
  - subscale of the Addiction Research Center Inventory (ARCI)
  - empirically developed
  - 16 true-false items
  - Sample Questions:
    - I feel more clear-headed than dreamy.
    - I feel a very pleasant emptiness.
    - My thoughts come more easily than usual.
    - I feel less discouraged than usual.

Single Dose Studies: Subjective Effect Profiles

- Prototypic Opioids
  - Morphine, heroin
  - Drug Effect/High
  - Liking
  - MBG* (euphoria)
  - PCAG* (sedation)
  - Nodding
  - Identified as Opiate
- Non-morphine-like Opioids
  - Nalorphine, cyclazocine
  - Drug Effect/High
  - no Liking
  - LSD* (dysphoria)
  - PCAG* (sedation)
  - Drunk
  - Nervous
  - Identified as Barbiturate

* Subscales of the ARCI

Heroin, Morphine, Methadone

Objective

Subjective

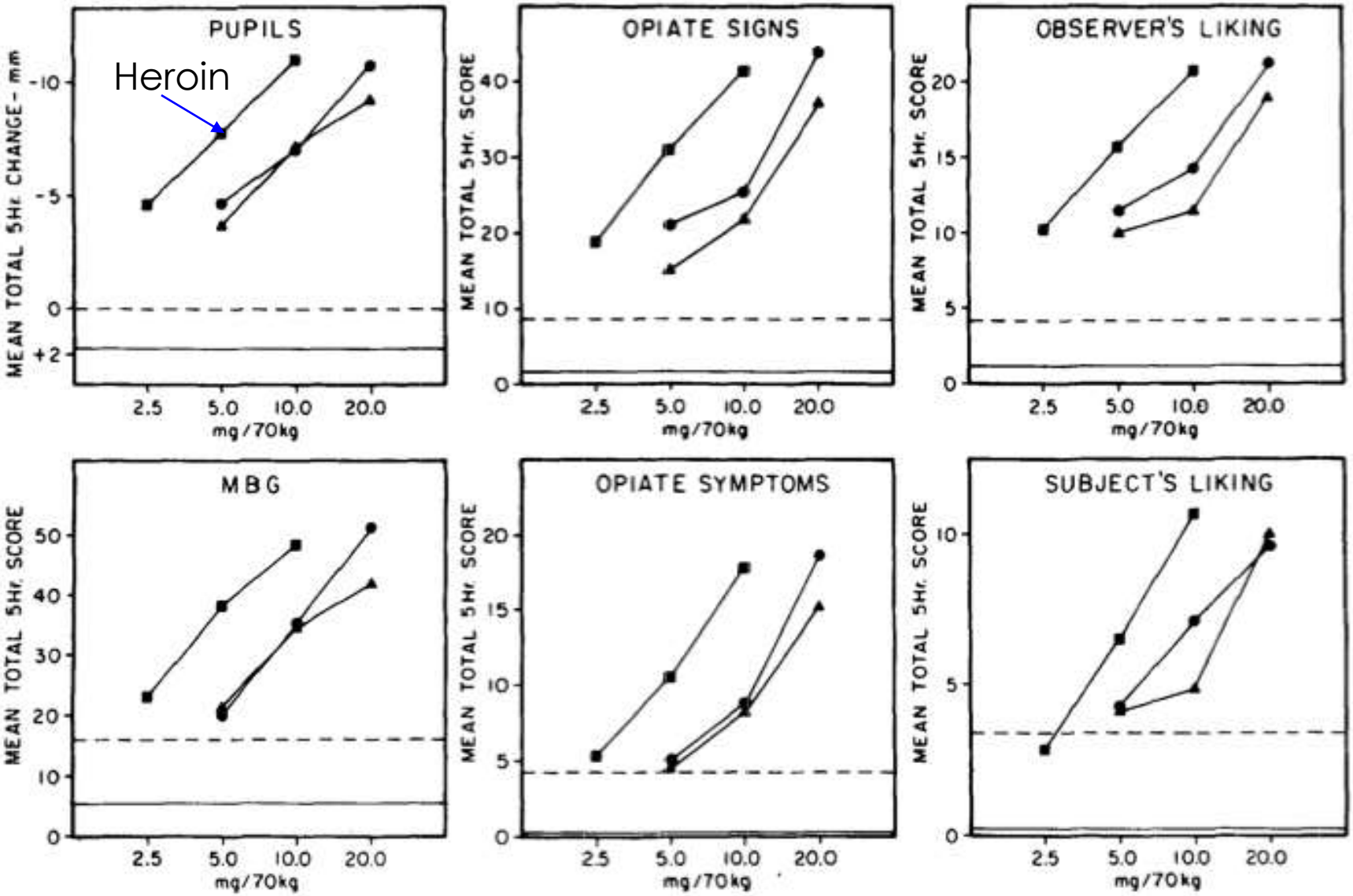
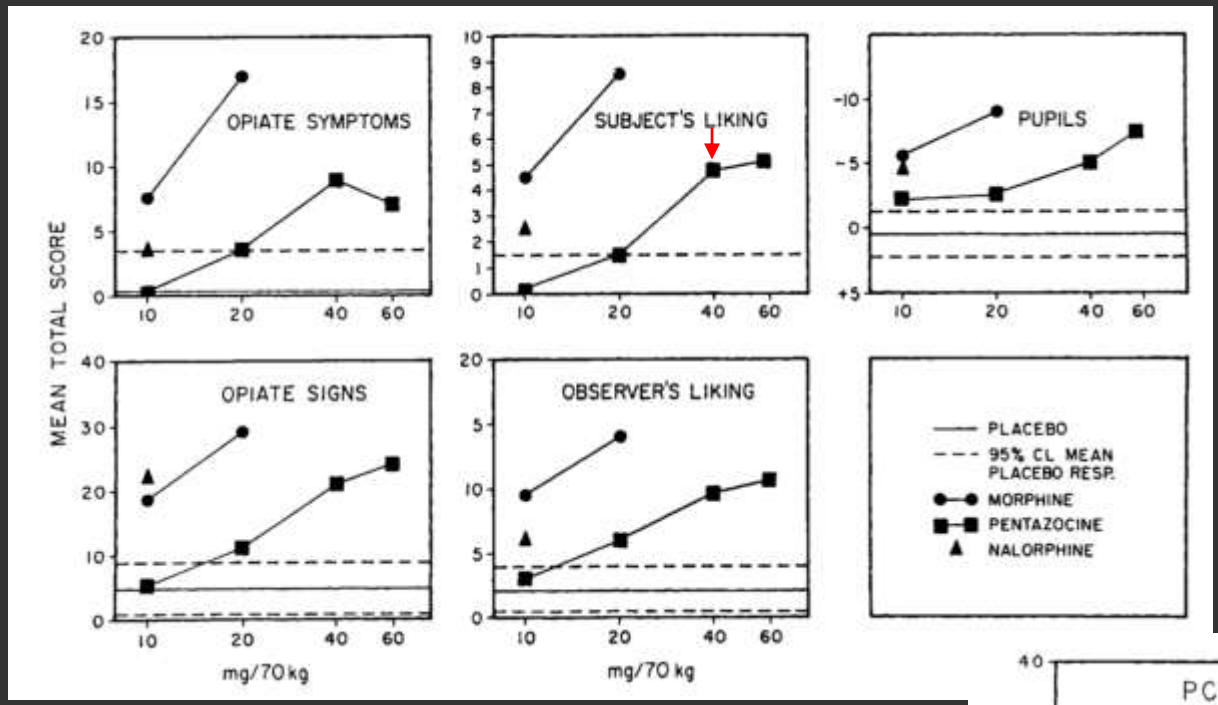


Fig. 2. Dose effect curves using 5-h total scores for pupillary change, opiate signs, observers' liking, MBG, opiate symptom and subjects' liking scores for the comparison of intravenously administered heroin, morphine and placebo. Morphine (M) (•——•); methadone (ME) (▲——▲); heroin (H) (■——■); placebo (——); 95% confidence limits/mean placebo response (– – –).

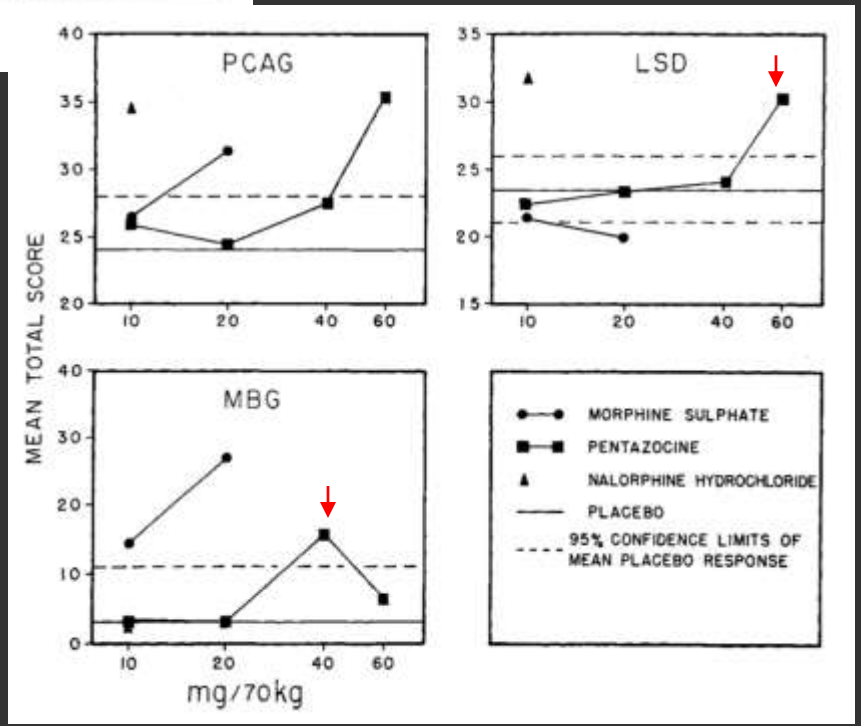
Intravenous administration; N = 9

Jasinski & Preston, DAD, 1986

Morphine, Pentazocine, Nalorphine



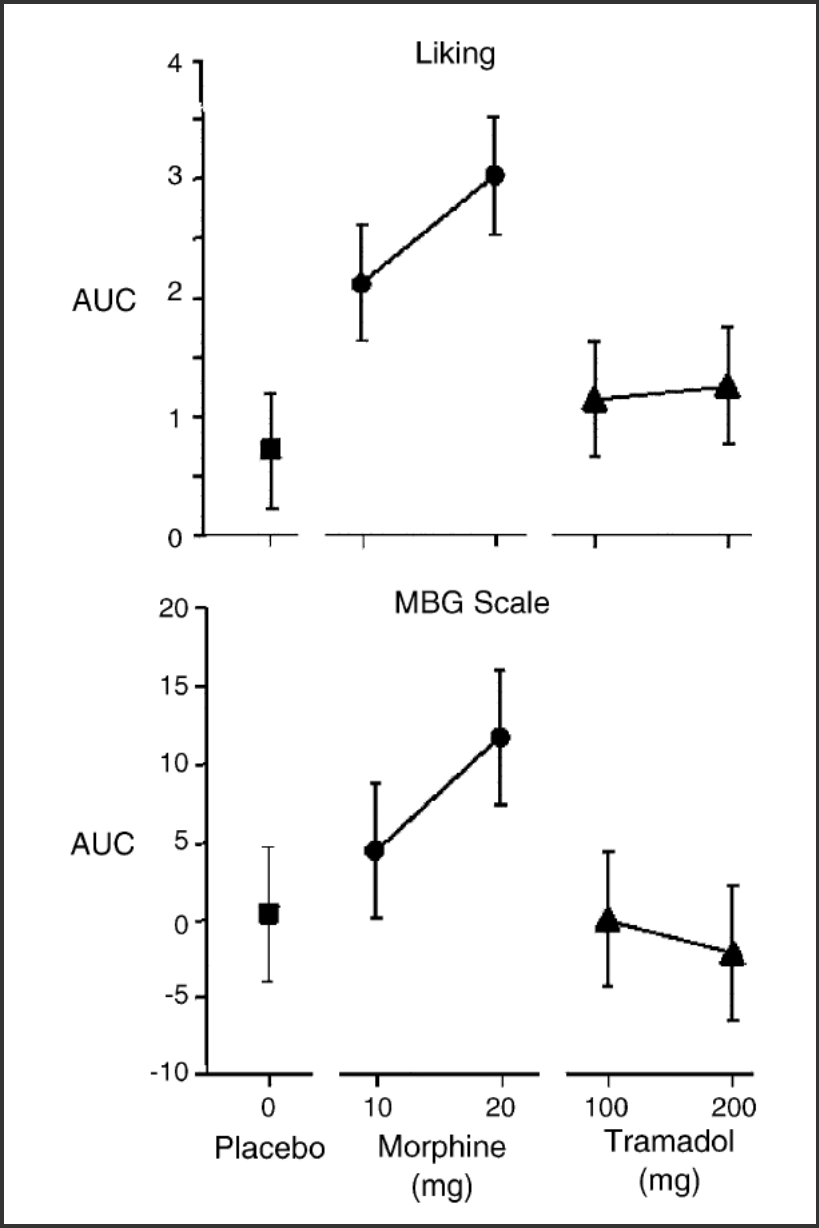
Subcutaneous Administration
N=12



Jasinski, Martin & Hoeldtke, Clin Pharm Ther 11, 385-403, 1970

Tramadol vs. Morphine

Intramuscular administration

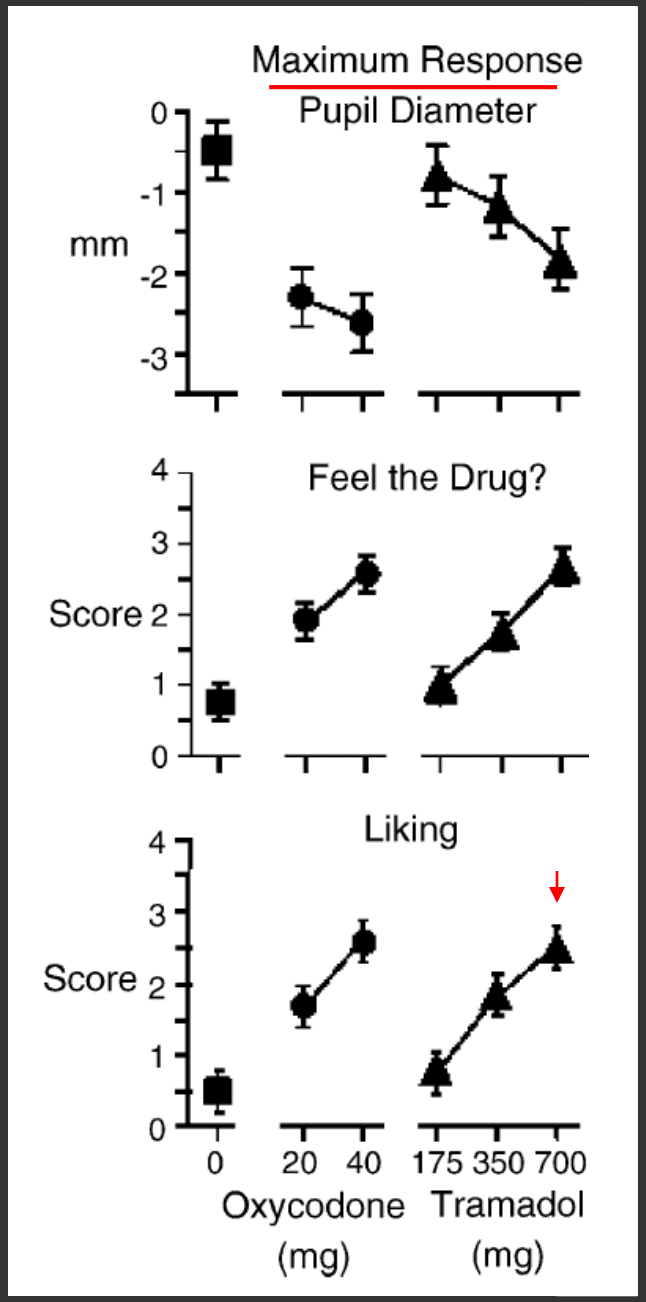


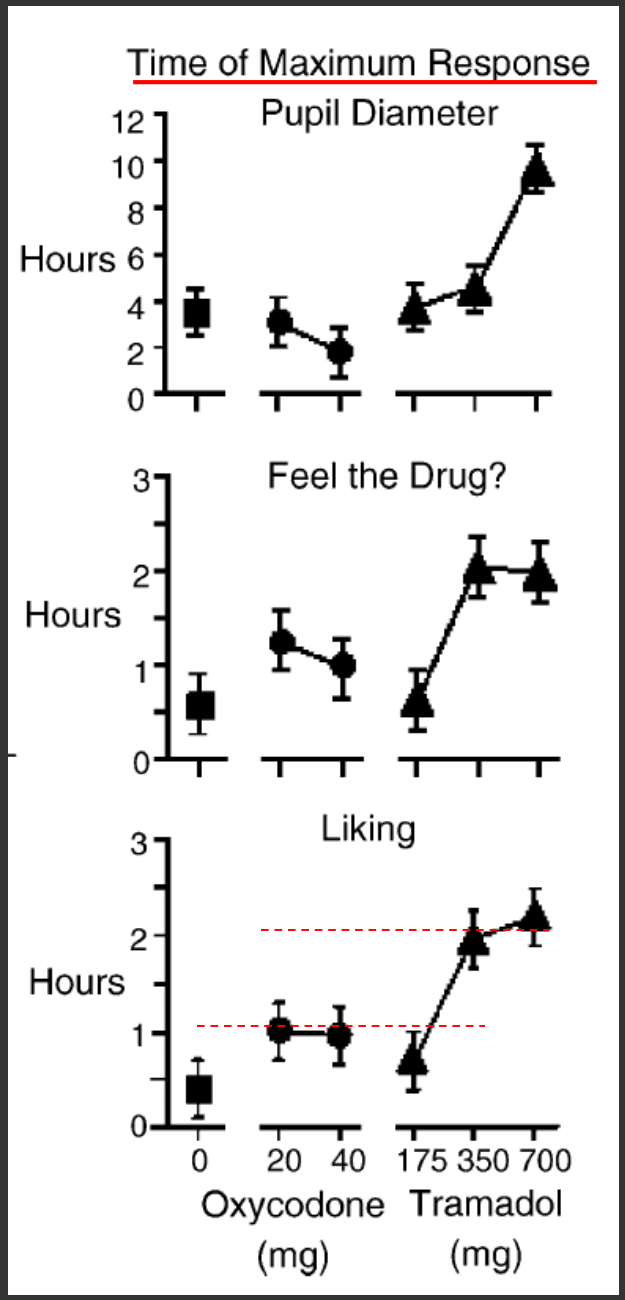
Preston, Jasinski, Testa, DAD 1991

Tramadol vs. Oxycodone

Oral Administration

N = 12





Epstein, Preston, Jasinski, Biol Psychol, 2006

Drug and Alcohol Dependence 129 (2013) 116–124

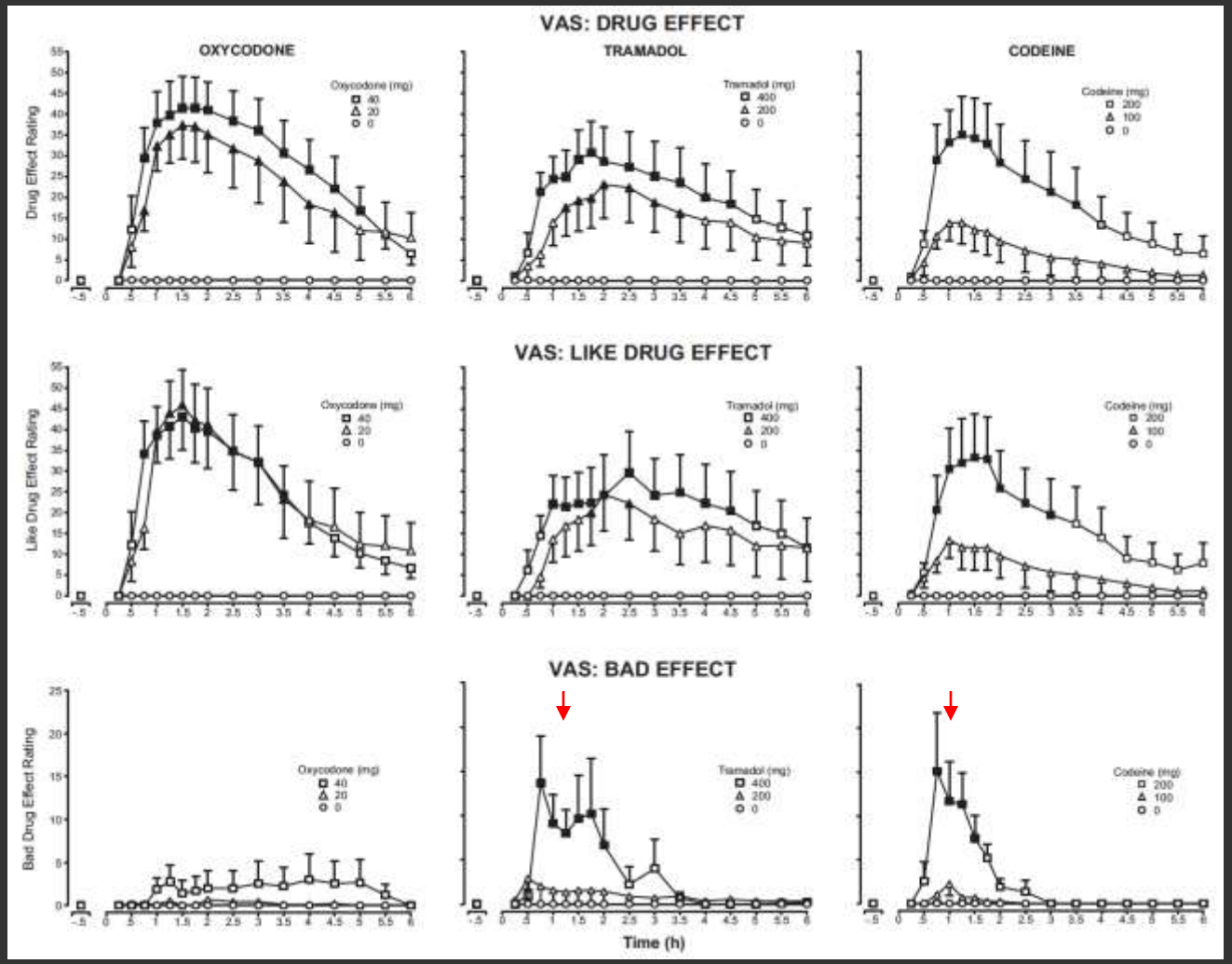
Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Abuse liability and reinforcing efficacy of oral tramadol in humans

Shanna Babalonis[a,b,*], Michelle R. Lofwall[a,b,c], Paul A. Nuzzo[b], Anthony J. Siegel[c], Sharon L. Walsh[a,b,c,d]



Dependence Potential

"Single dose studies"

Self-administration

Drug Discrimination

Self Administration

Participants are given the opportunity to take drug in the laboratory

A behavioral response is often required to earn a drug dose
- Work requirement may increase with each dose (progressive ratio)
- Breakpoint - point at which participants stops earning doses

Often an alternative reinforcer is available (another drug, money, or food)

Outcome measure can be the proportion of test drug doses chosen or the breakpoint

Two phases: Sampling, self-administration

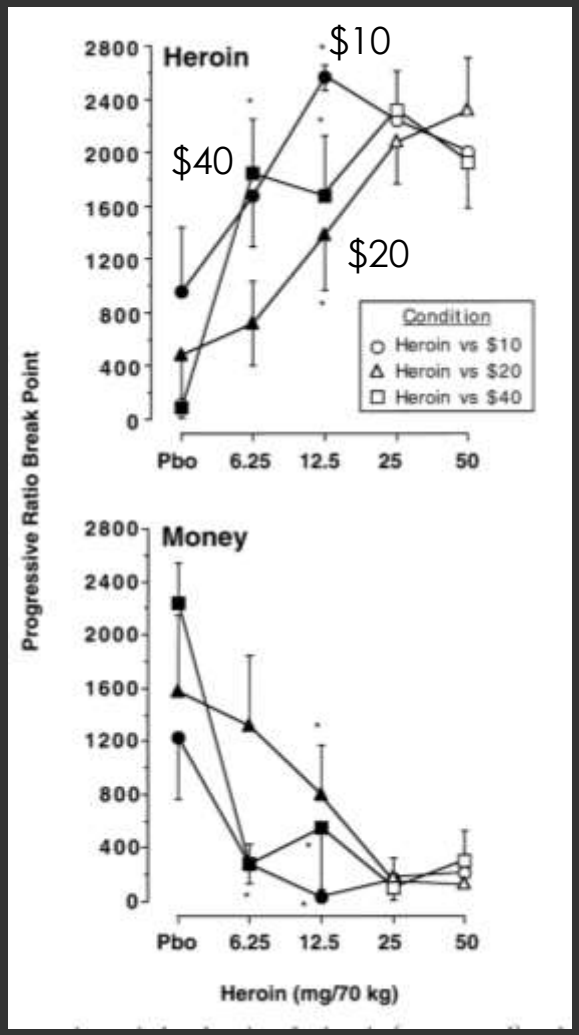
Other types of measures can be collected concurrently: subjective, physiological, pharmacokinetic

Effects of an alternative reinforcer on intravenous heroin self-administration by humans

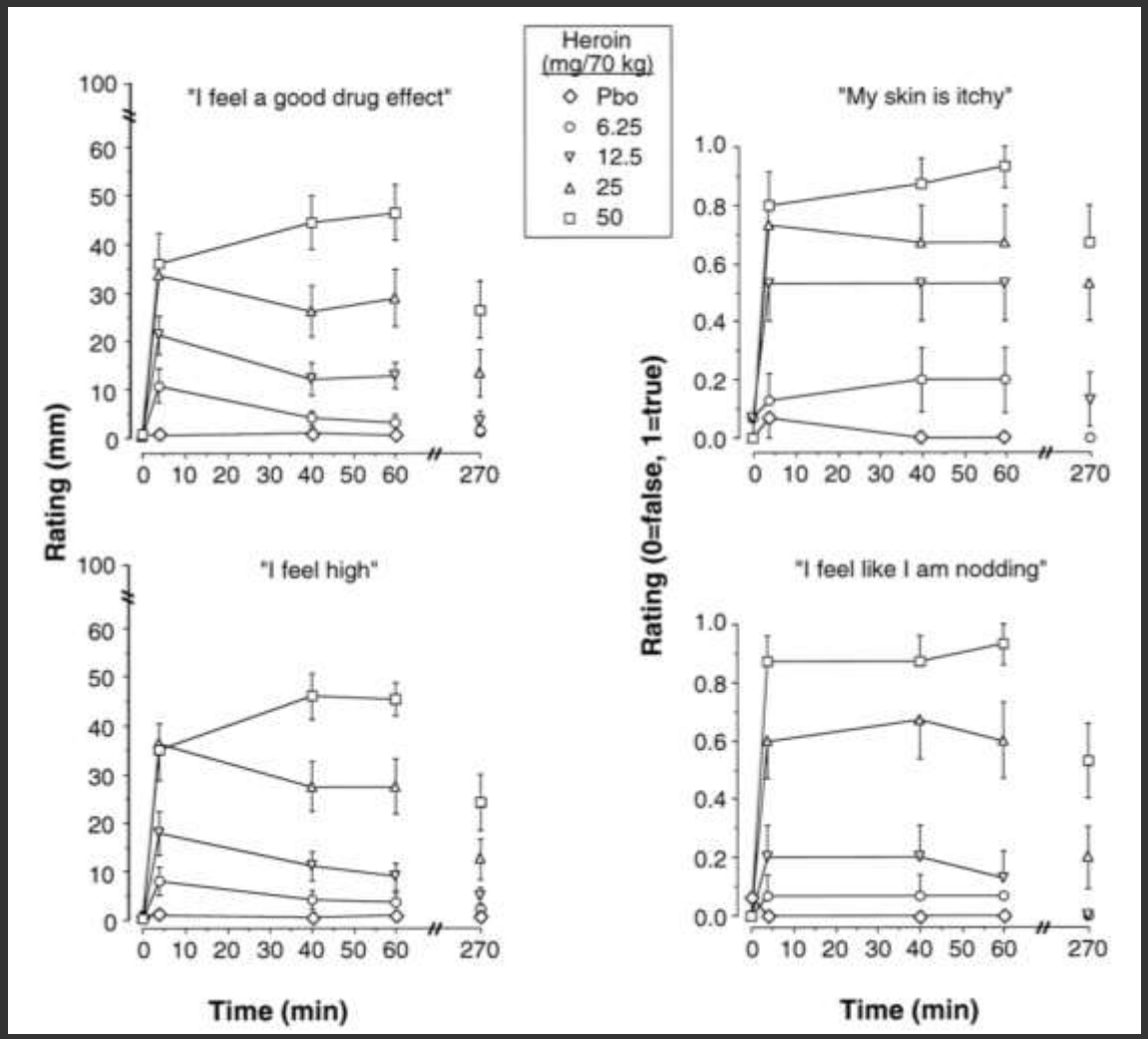
Sandra D. Comer *, Eric D. Collins, Scott T. Wilson, Michael R. Donovan, Richard W. Foltin, Marian W. Fischman

European Journal of Pharmacology 345 (1998) 13–26

Dose response for heroin at 3 monetary alternatives
Ppts were maintained for oral morphine 20-40 mg q.i.d.; N = 5



Self-Administration Sessions



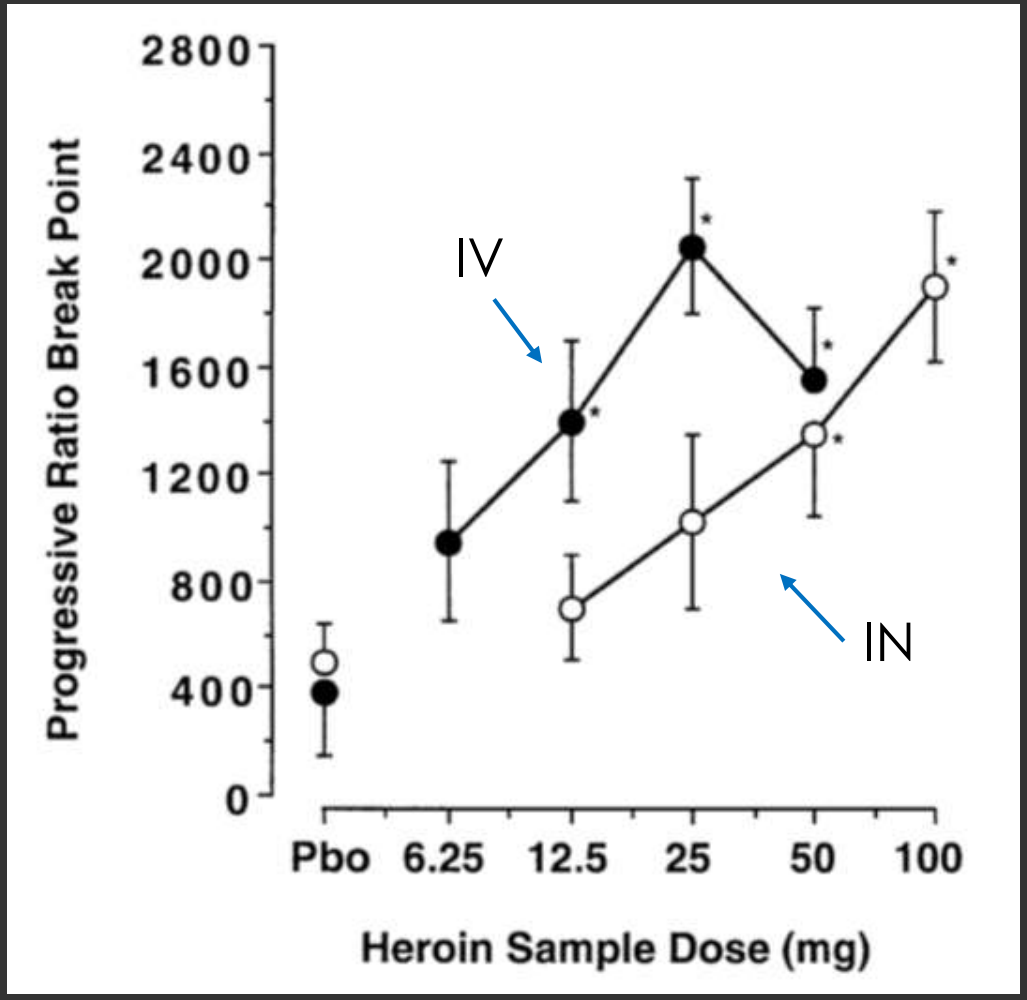
Sampling Sessions – Subjective Effects

Psychopharmacology (1999) 143 : 327–338

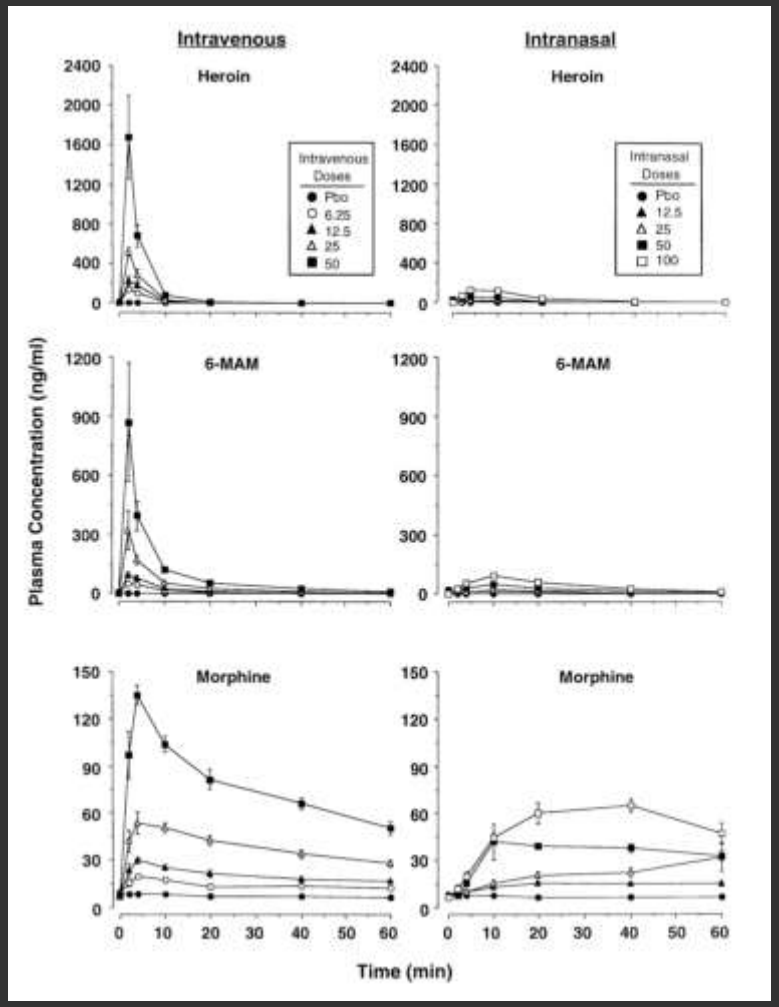
ORIGINAL INVESTIGATION

Sandra D. Comer · Eric D. Collins
Robert B. MacArthur · Marian W. Fischman

Comparison of intravenous and intranasal heroin self-administration by morphine-maintained humans



Self-Administration Sessions



Sampling Sessions - Pharmacokinetics

Drug and Alcohol Dependence 129 (2013) 116–124

Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Abuse liability and reinforcing efficacy of oral tramadol in humans

Shanna Babalonis[a,b,*], Michelle R. Lofwall[a,b,c], Paul A. Nuzzo[b], Anthony J. Siegel[c], Sharon L. Walsh[a,b,c,d]

N = 9

Participants –

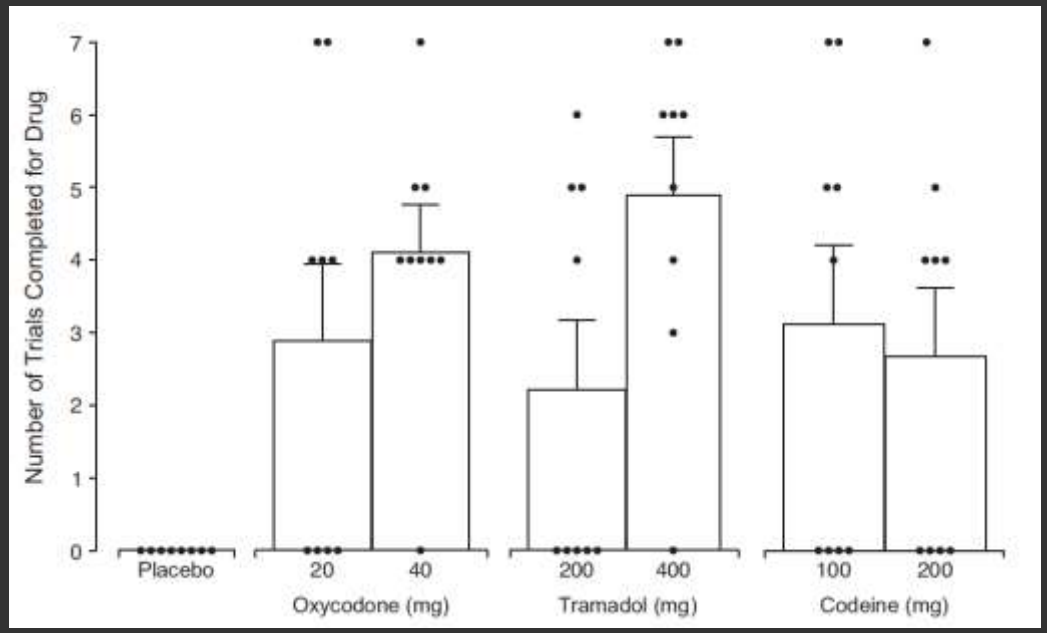
- not dependent
- histories of prescription opioid abuse

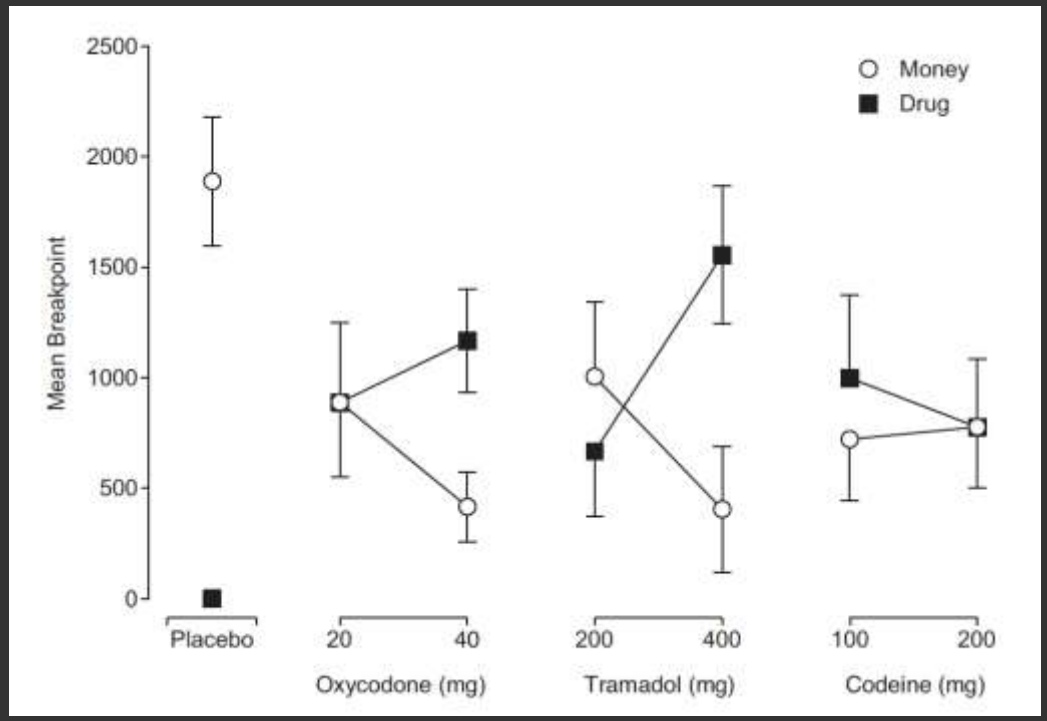
14 paired sessions

- 7 sampling (subjective effect measures)
- 7 self-administration

Choice - work for drug or money

Progressive ratio





Dependence Potential

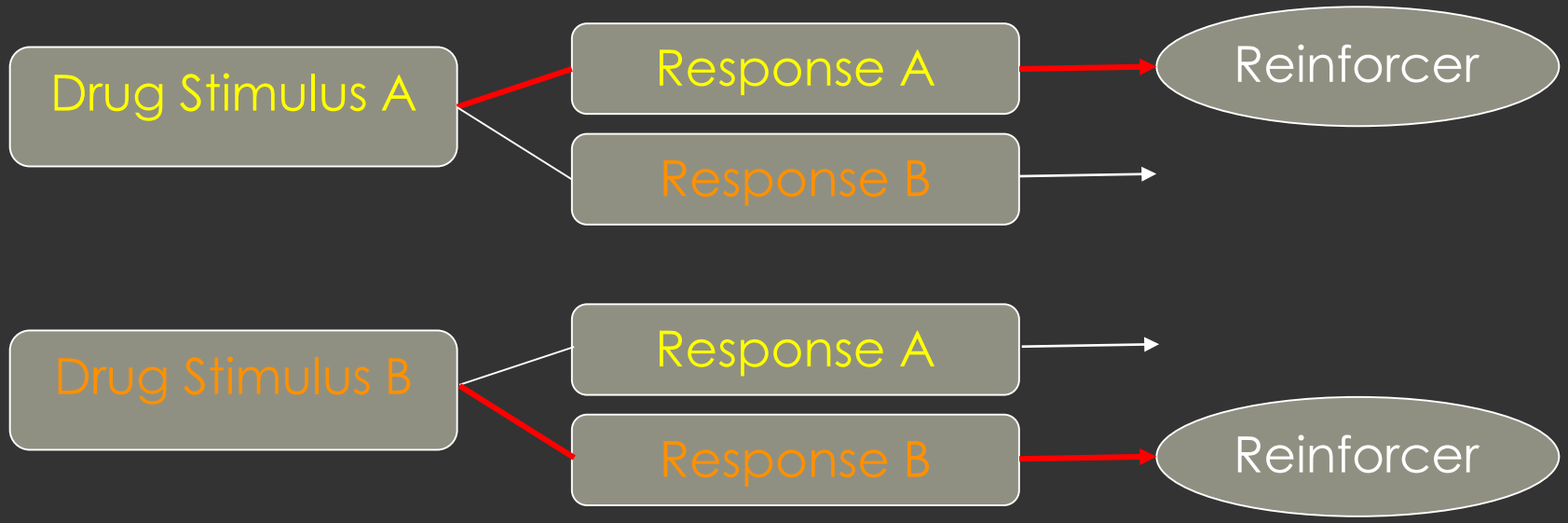
"Single dose studies"

Self-administration

Drug Discrimination

Drug Discrimination

Participants learn to identify the presence of one or more training (or prototypic) drug(s)



Novel drug is then tested to determine if participants identify it as the training drug

Other types measures can be collected concurrently

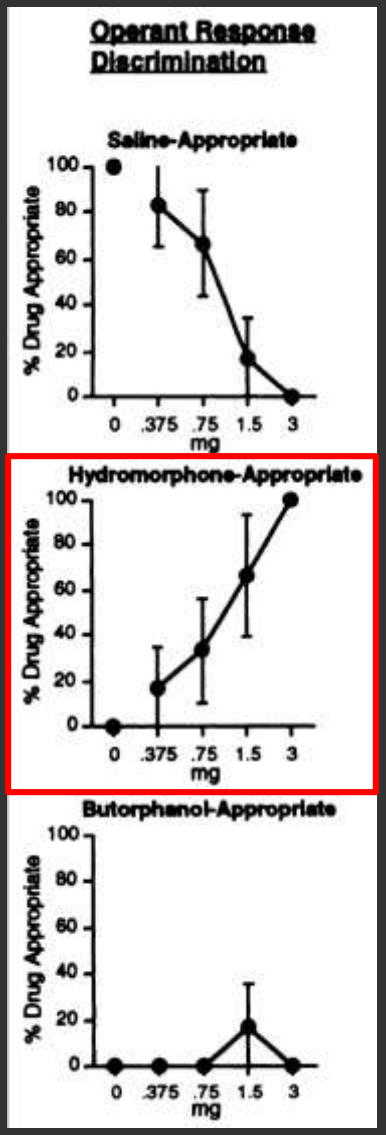
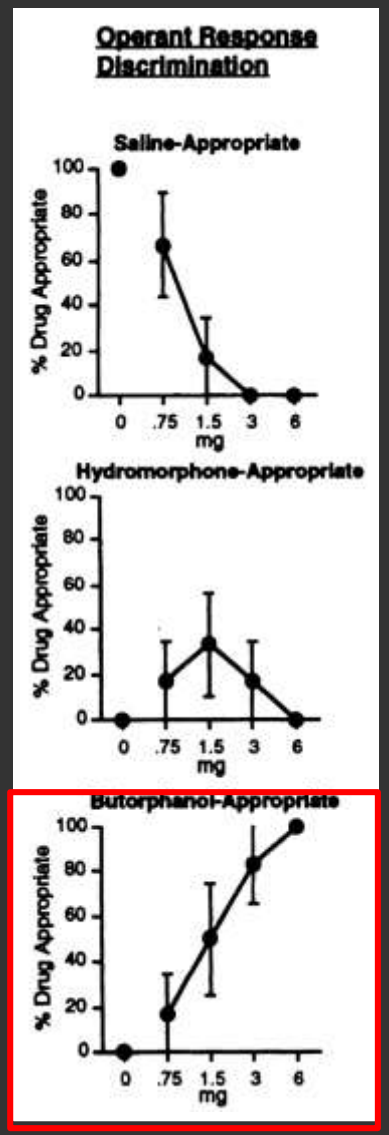
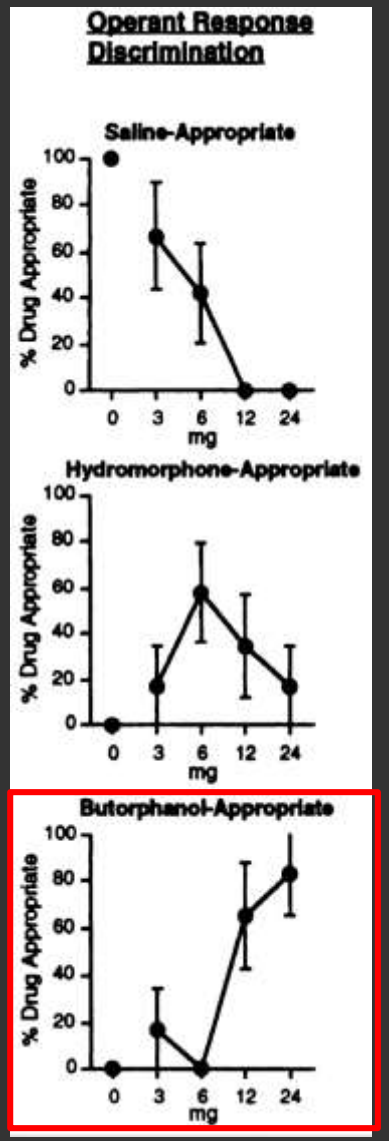
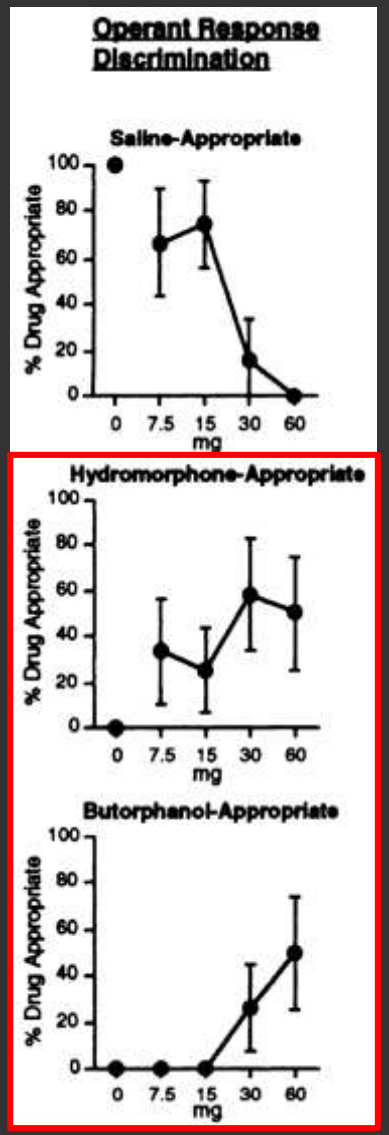
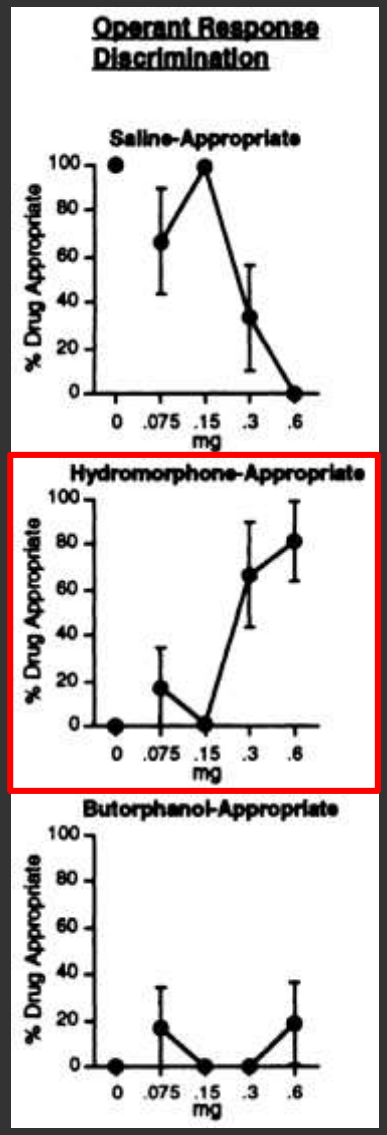
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 1994 by The American Society for Pharmacology and Experimental Therapeutics
JPET 271:40–46, 1994
Vol. 271, No. 1
Printed in U.S.A.

Drug Discrimination Assessment of Agonist-Antagonist Opioids in Humans: A Three-Choice Saline-Hydromorphone-Butorphanol Procedure[1]

KENZIE L. PRESTON and GEORGE E. BIGELOW

Training conditions:
Saline
Hydromorphone 3 mg
Butorphanol 6 mg

N = 6

Hydromorphone	Butorphanol	Nalbuphine	Pentazocine	Buprenorphine
				

0022-3565/11/3381-255–262$25.00
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Copyright © 2011 by The American Society for Pharmacology and Experimental Therapeutics
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Vol. 338, No. 1
181131/3666035
Printed in U.S.A.

Discriminative Stimulus Effects of Tramadol in Humans

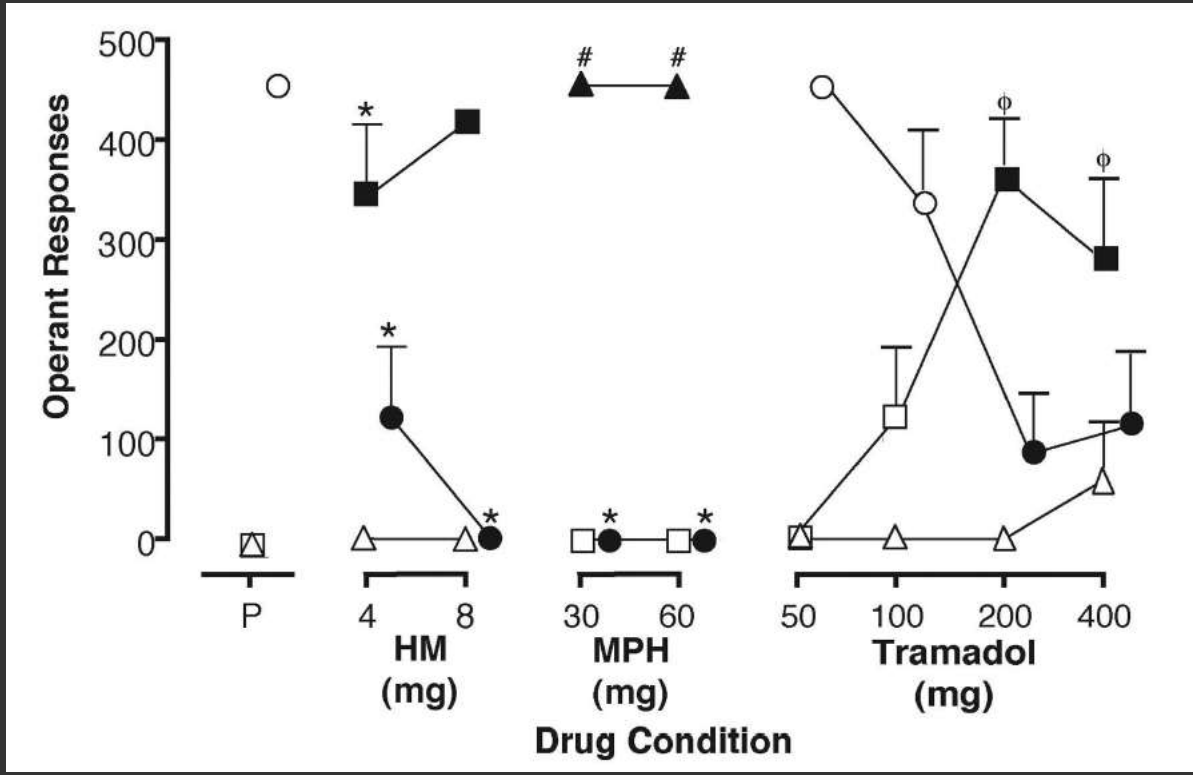
Angela N. Duke, George E. Bigelow, Ryan K. Lanier, and Eric C. Strain

Training drugs:

Hydromorphone, Methylphenidate, placebo

Identified by letter codes

N = 8, non-dependent, histories of opioid and stimulant use



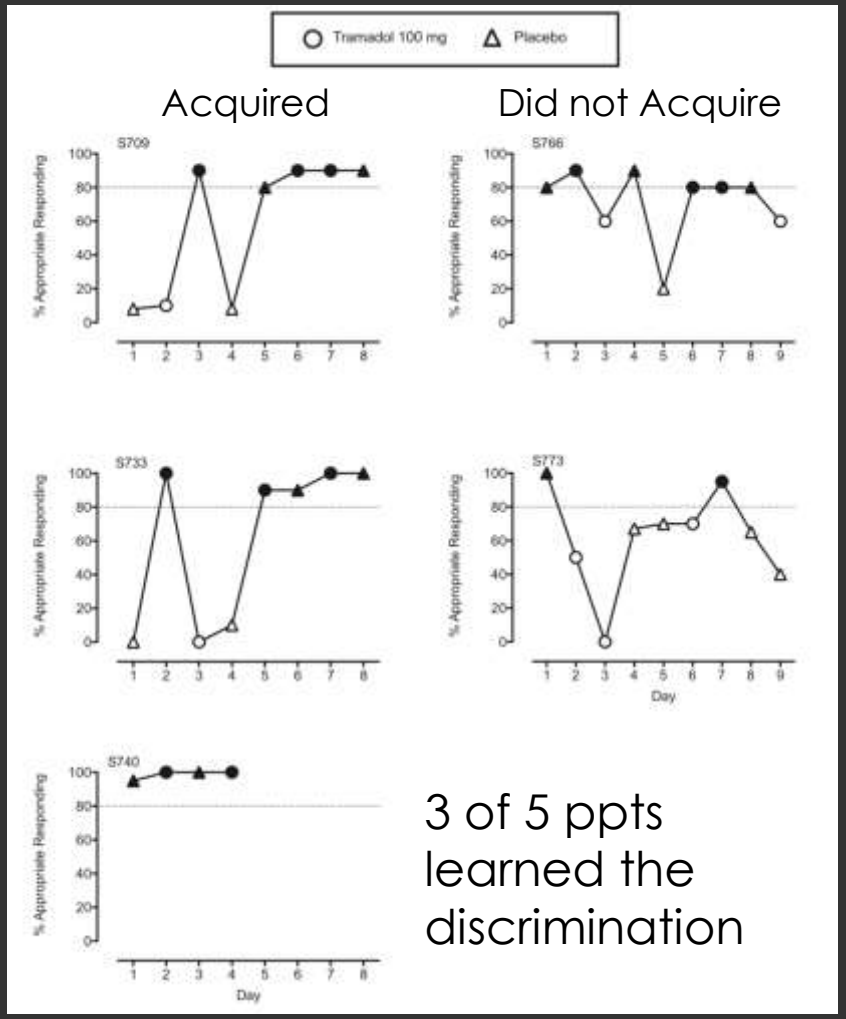
JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR 2015, **103**, 361–374 NUMBER 2 (MARCH)

MU OPIOID MEDIATED DISCRIMINATIVE-STIMULUS EFFECTS OF TRAMADOL: AN INDIVIDUAL SUBJECTS ANALYSIS

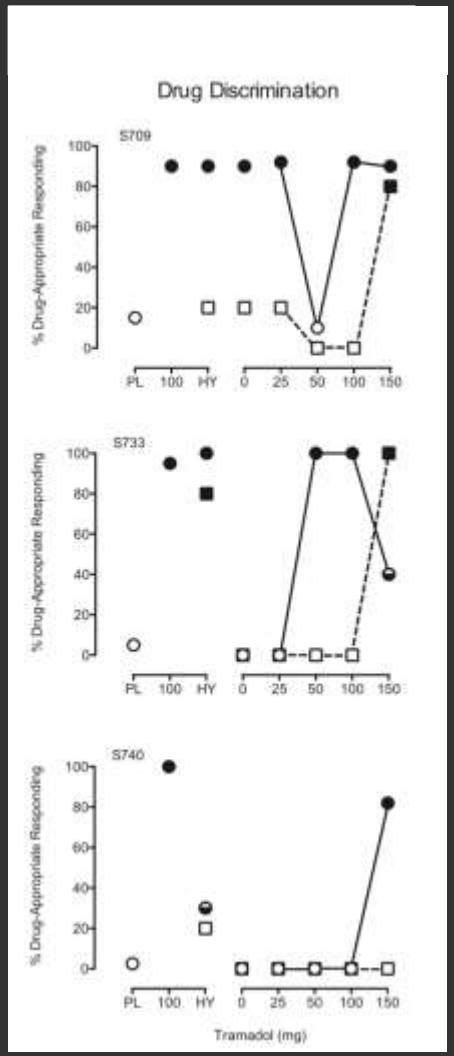
JUSTIN C. STRICKLAND[1], CRAIG R. RUSH[1,2,3], AND WILLIAM W. STOOPS[1,2,3]

Tramadol 100 mg vs Placebo

Drug A vs. Not Drug A



3 of 5 ppts learned the discrimination



2 of 3 discriminated hydromorphone 4 mg as tramadol

Pretreatment with naltrexone 50 mg shifted the dose response to the right,

Results suggest that discrimination was based on mu opioid effects.

Advantages and Disadvantages

Single Dose (Acute Effects) studies

Advantages:

- Methods well established
- Few sessions required – easier to do a dose response curve

Disadvantages:

- Relies on subjective measures
- Need to interpret across many measures

Self-administration

Advantages:

- Face validity (drug-taking is what we are generally concerned about)
- Behavioral measure – objective (not subjective)
- Other measures, like self-report, can be collected

Disadvantages:

- Takes more sessions than "single dose studies"
- Harder to get right than it seems
- Lots of factors affect participants' decisions

Drug Discrimination

Advantages:

- Behavioral measure – objective (not subjective)
- Gives one answer to similarity (assimilates effects on divergent measures)
- Other measures, like self-report, can be collected

Disadvantages:

- Takes many more sessions than "single dose studies"
- Choice of training drugs/doses affect results

Risk Assessment

Adverse Events

Dependence Potential

Opioid Antagonist Activity

Will administration precipitate withdrawal symptoms in a patient taking opioid agonists

Physical Dependence Potential

The American Journal on Addictions

Full Access

Treatment of Buprenorphine Precipitated Withdrawal: A Case Report

Didier Jutras-Aswad MD, MS, Michelle Widlitz MD, Michael M. Scimeca MD

American Journal of Therapeutics 22, 199–205 (2015)

Transdermal Buprenorphine, Opioid Rotation to Sublingual Buprenorphine, and the Avoidance of Precipitated Withdrawal: A Review of the Literature and Demonstration in Three Chronic Pain Patients Treated With Butrans

Howard Kornfeld, MD, FASAM[1,2,3]* and Heidi Reetz, MD[4]

ELSEVIER

Journal of Substance Abuse Treatment

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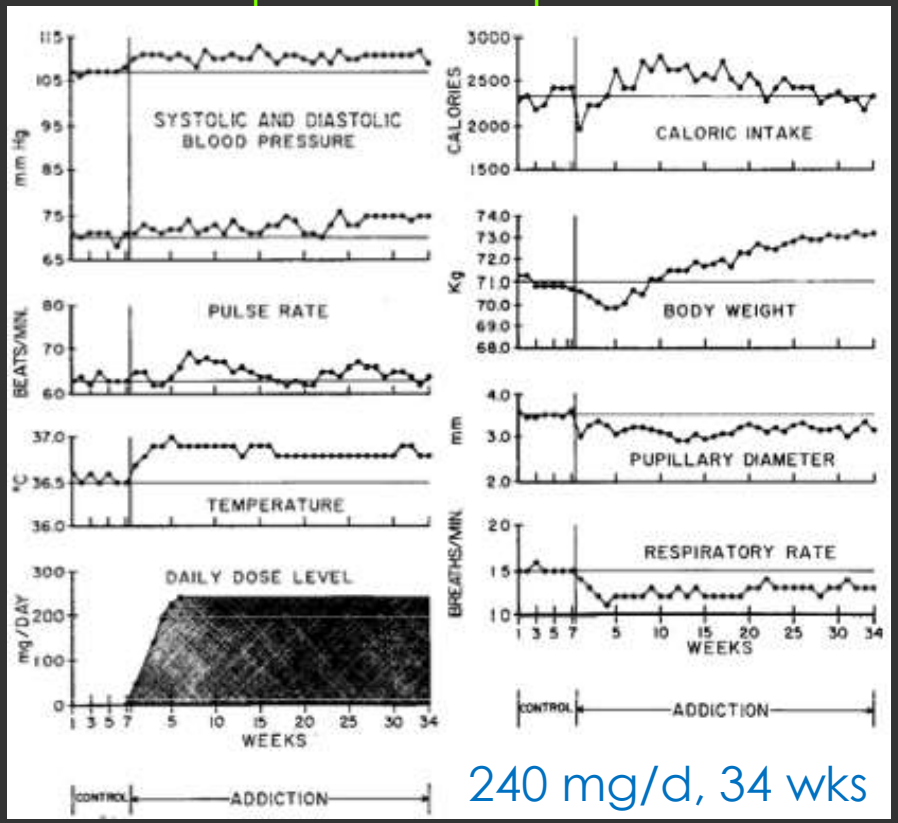
Regular article

Factors associated with complicated buprenorphine inductions

Susan D. Whitley M.D. [a] ✉, Nancy L. Sohler Ph.D., M.P.H. [b, c], Hillary V. Kunins M.D., M.P.H., M.S. [c], Angela Giovanniello Pharm.D. [c], Xuan Li M.S. [c], Galit Sacajiu M.D., M.P.H. [c], Chinazo O. Cunningham M.D., M.S. [c]

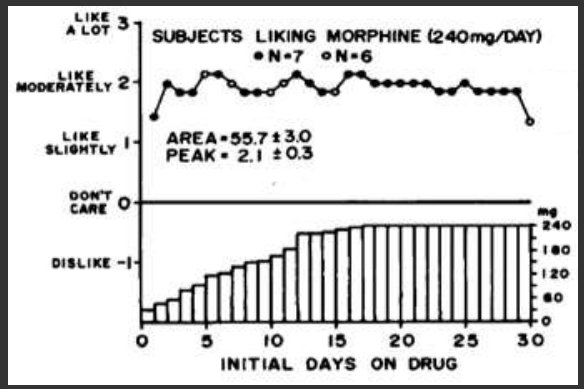
Opioid Physiological Dependence and Withdrawal

Repeated Morphine



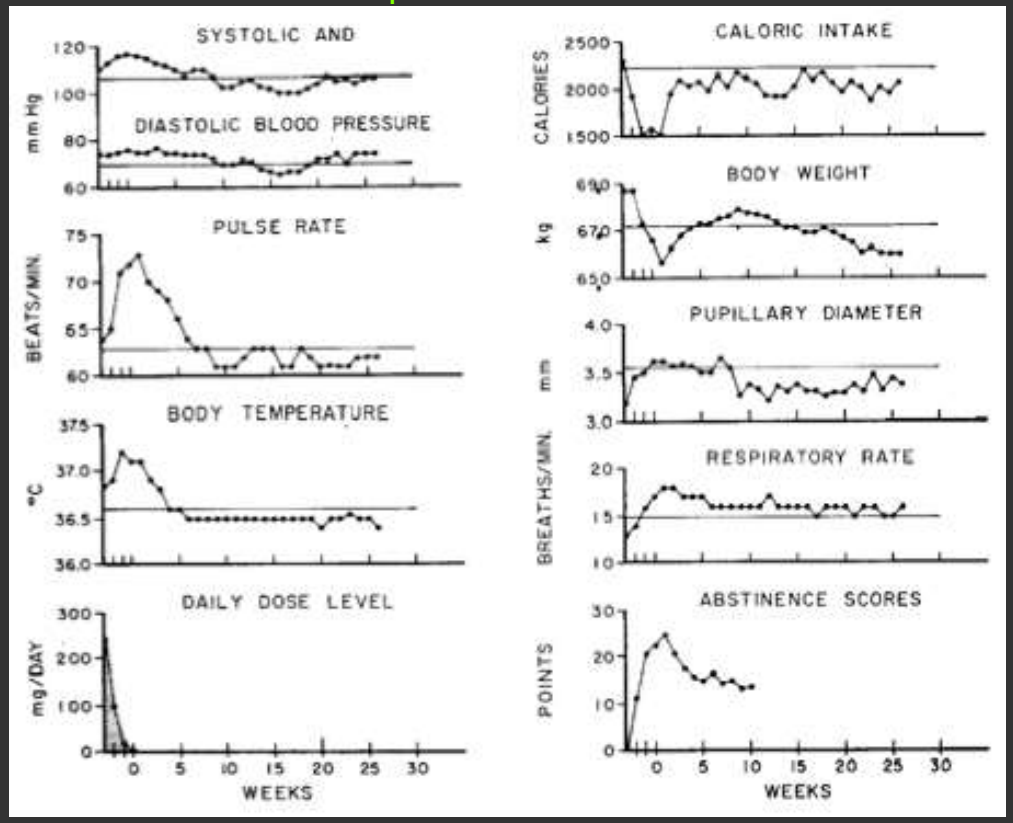
240 mg/d, 34 wks

Martin and Jasinski, J Psychiat Res 1969



Jasinski et al., Archives Gen Psychiatry 1978

Abrupt Discontinuation



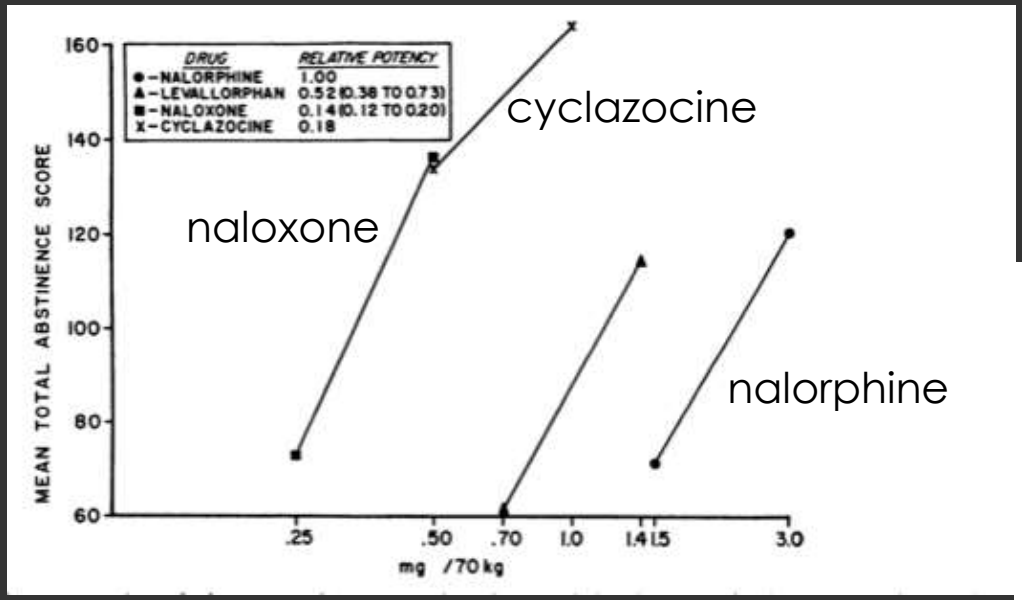
Symptoms

Restless, irritability
Nausea, cramps
Muscle aches
Dysphoric mood
Insomnia, anxiety
Craving for opioids

Signs

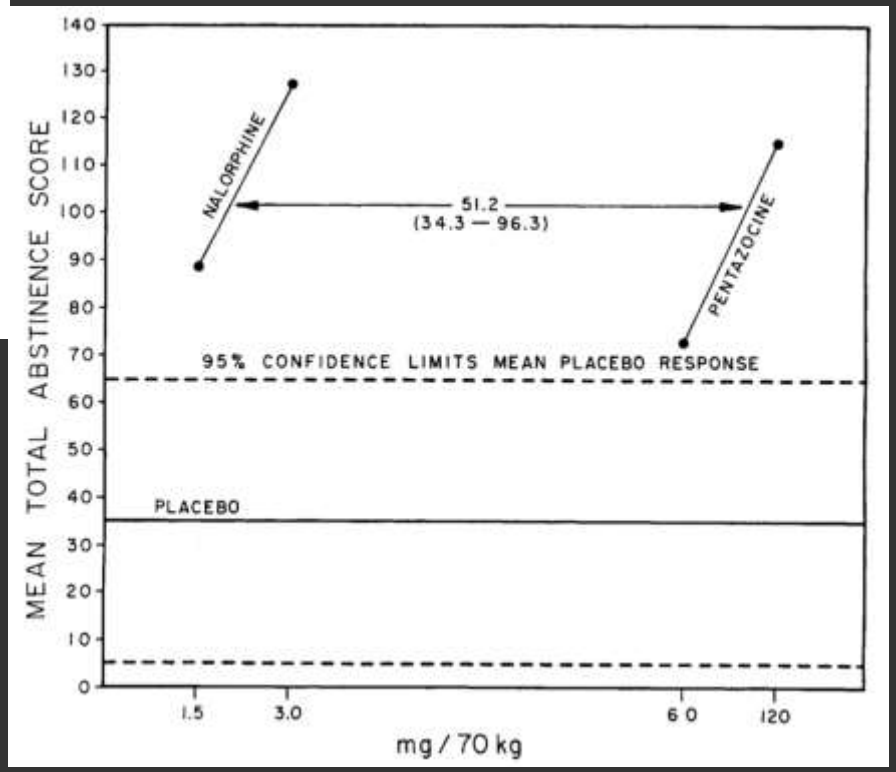
Pupillary dilation
Sweating
Piloerection ("gooseflesh")
Tachycardia
Vomiting, diarrhea
Increased blood pressure
Yawning

Drugs with Opioid Antagonist Activity Produce Withdrawal in Opioid-Dependent Patients



Jasinski et al. JPET 1967

Precipitated abstinence syndrome in subjects receiving morphine 240 mg/d



Jasinski, Martin & Hoeldtke, Clin Pharm Ther 1970

Experimental and Clinical Psychopharmacology
2006, Vol. 14, No. 2, 109–120

1064-1297/06/$12.00 DOI: 10.1037/1064-1297.14.2.109

Assessment of Agonist and Antagonist Effects of Tramadol in Opioid-Dependent Humans

C. Patrick Carroll, Sharon L. Walsh, George E. Bigelow, and Eric C. Strain
Johns Hopkins University School of Medicine

Kenzie L. Preston
National Institute on Drug Abuse

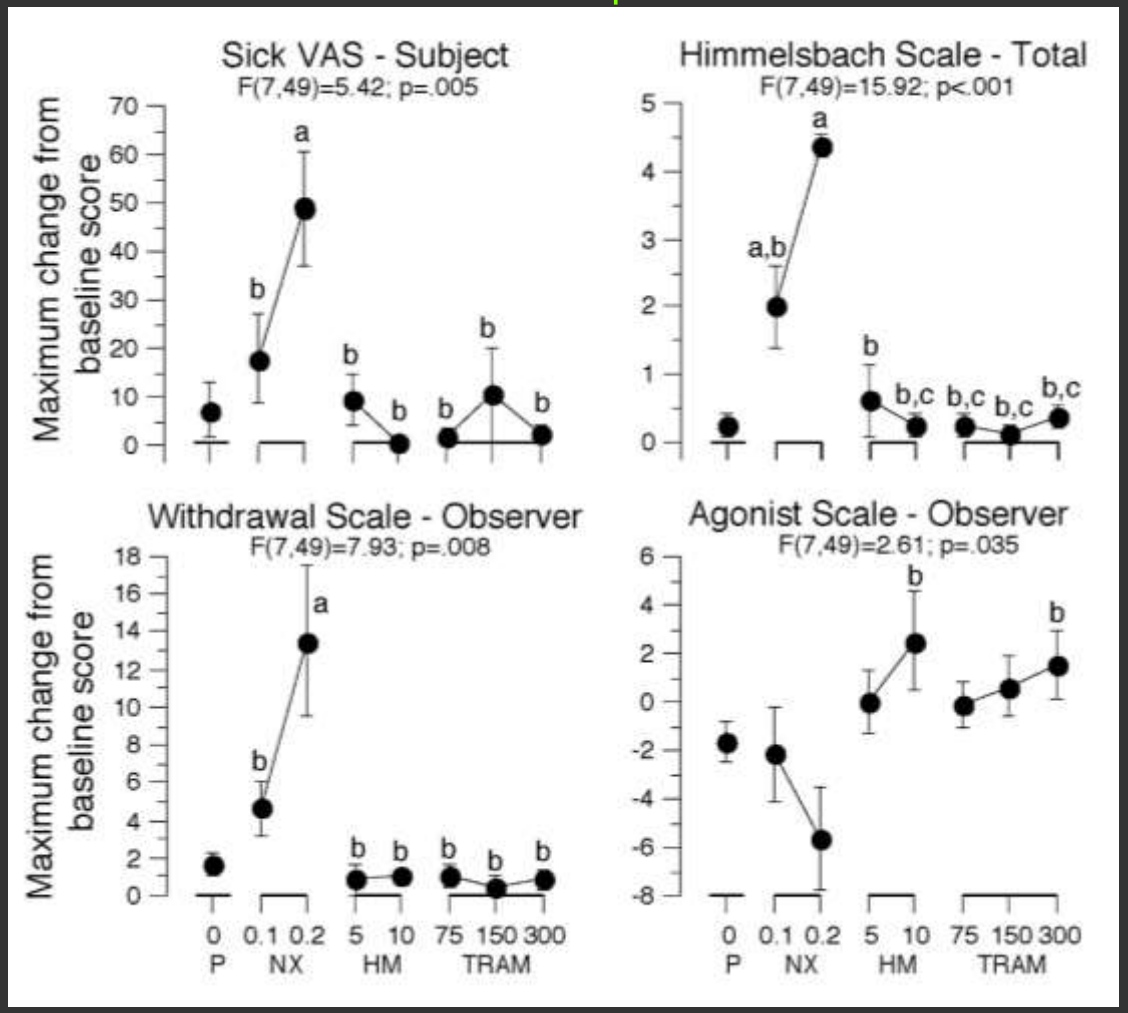
Withdrawal Precipitation Test

Ppts receiving methadone 60 mg/d

Tested 20 hr after last methadone dose

N = 8

Test drugs
- placebo
- naloxone (NX)
- hydromorphone (HM)
- tramadol (TRAM)



Tramadol
- no withdrawal
- some agonist effects

Risk Assessment

Adverse Events

Dependence Potential

Opioid Antagonist Activity

Physical Dependence Potential

Will repeated administration lead to a discontinuation syndrome that could make stopping treatment difficult and/or unpleasant for patients

Substitution/Withdrawal Suppression Studies

Alternative to direct addiction studies

Test drugs are substituted for mu opioid agonists in participants receiving repeated administration.

-ARC studies, participants were maintained on morphine.

-More recently, other opioid agonists have been used

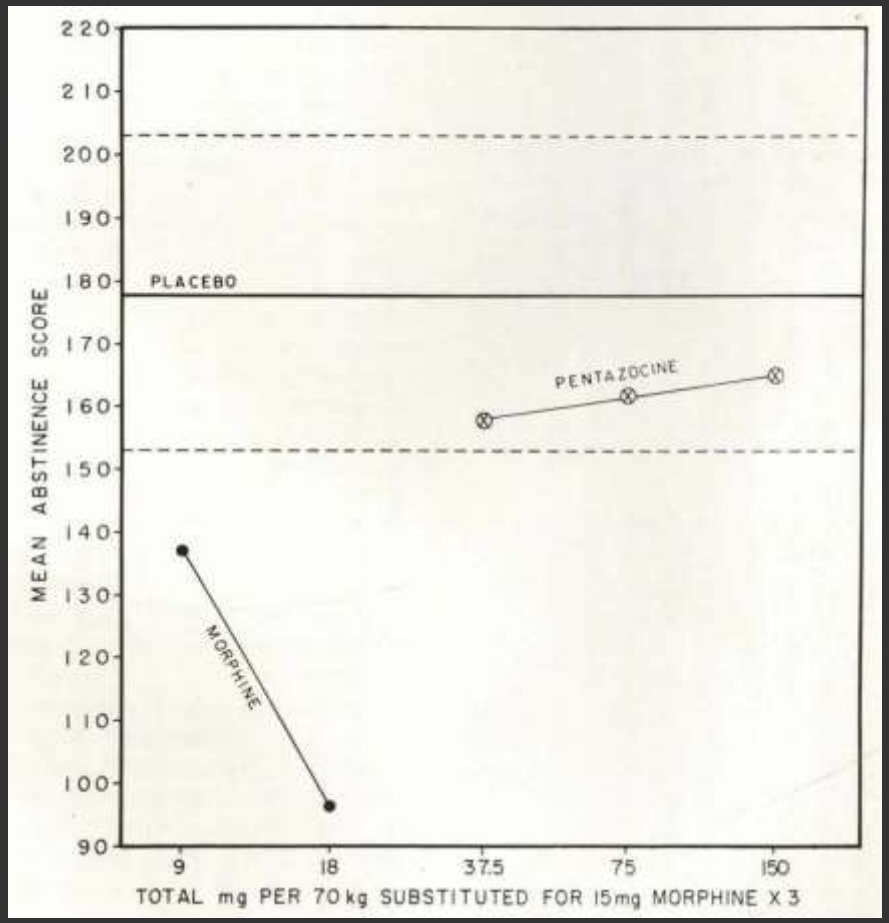
e.g., methadone and hydromorphone

Outcome measure is severity of opioid withdrawal.

Test drugs that suppress withdrawal are inferred to have mu agonist activity and may produce opioid dependence.

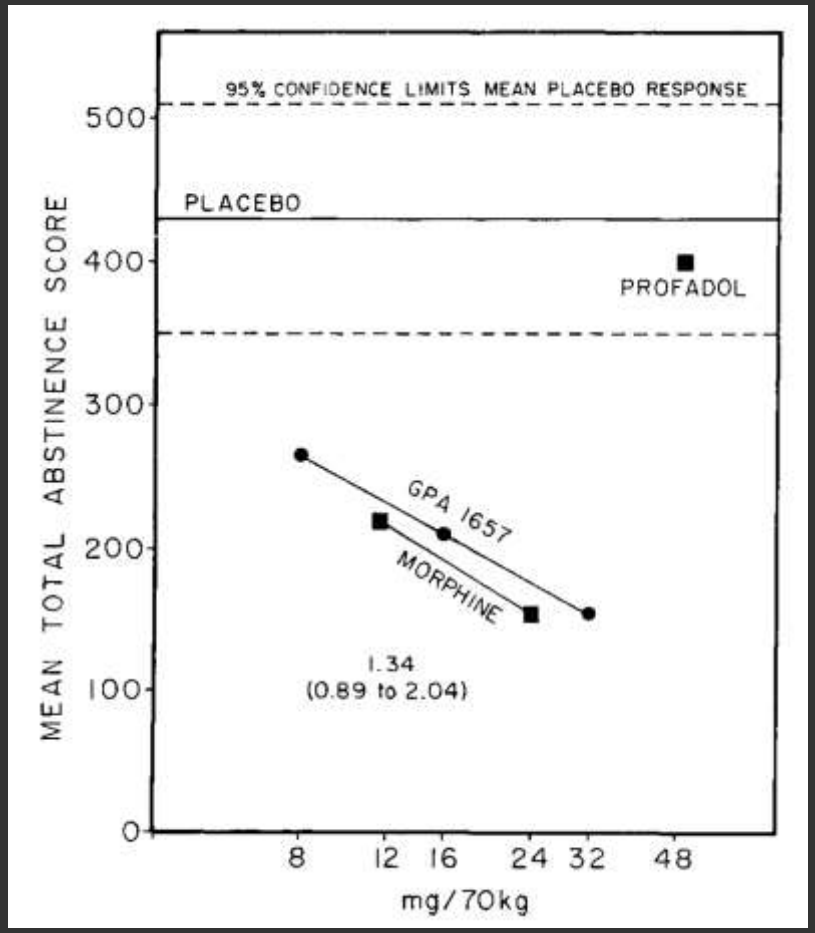
Substitution Studies

Pentazocine



Jasinski et al. Clin Pharm Ther 1970

GPA 1657 and Profadol



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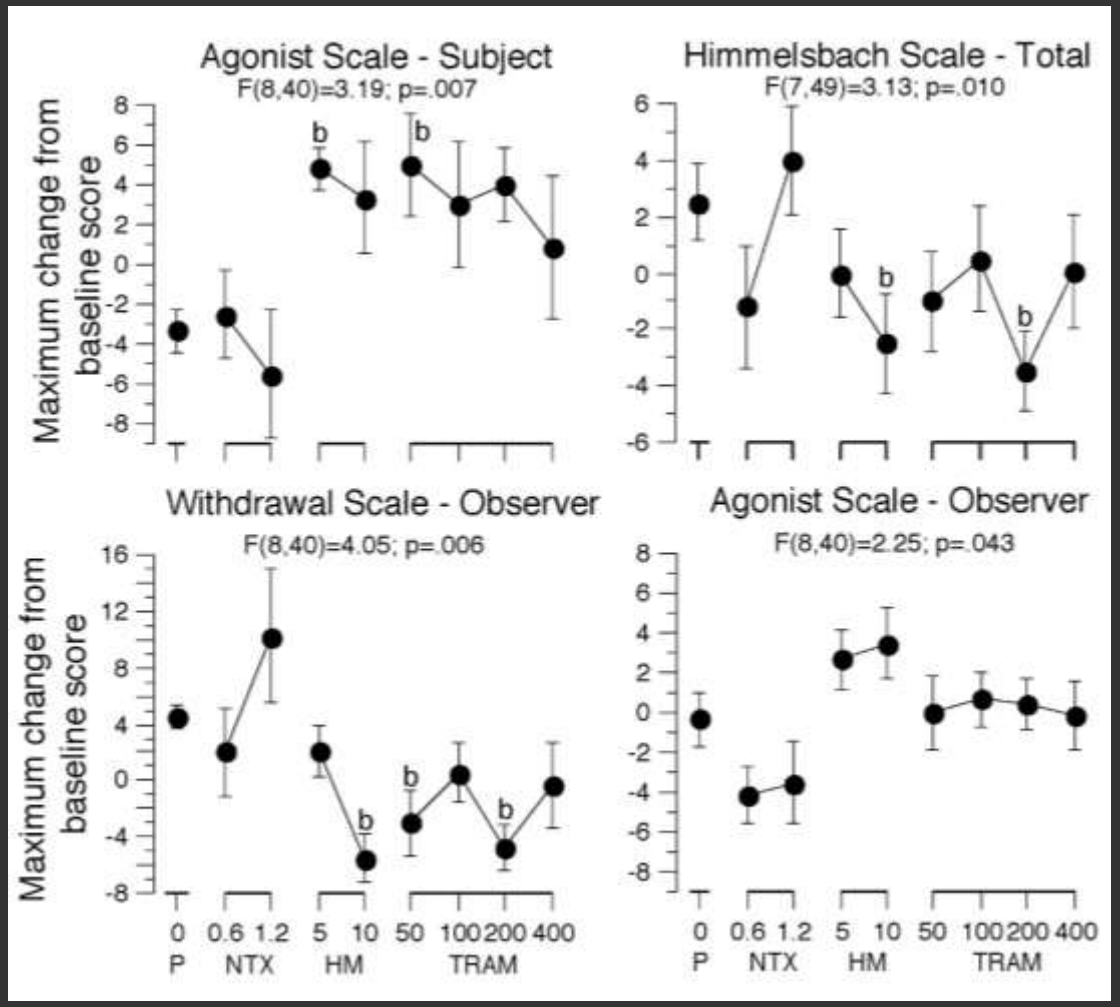
Withdrawal Suppression Test

Ppts receiving hydromorphone 10 mg q.i.d.

Tested 23 hr after last hydromorphone dose

N = 6

Tramadol reduced WD effects at some doses



Risk Assessment

Adverse Events
Dependence Potential
Opioid Antagonist Activity
Physical Dependence Potential

SYSTEMATIC REVIEW ARTICLE

Front. Psychiatry, 26 September 2019 | https://doi-org.ezproxy.nihlibrary.nih.gov/10.3389/fpsyt.2019.00704

A Systematic Review of Laboratory Evidence for the Abuse Potential of Tramadol in Humans

Kelly E. Dunn, Cecilia L. Bergeria, Andrew S. Huhn and Eric C. Strain

Conclusion: Taken together, individuals may be less likely than with other opioids to escalate tramadol doses, transition from oral to parenteral routes of administration, or continue using tramadol once opioid physical dependence develops. In that way, the human abuse potential of tramadol appears to be different from and lower than other opioid analgesic medications.

Questions?