Pharmacology of Fentanyl and Its Implications for Treatment of Opioid Use Disorder

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Department of Psychiatry
Columbia University
New York State Psychiatric Institute

Disclosures

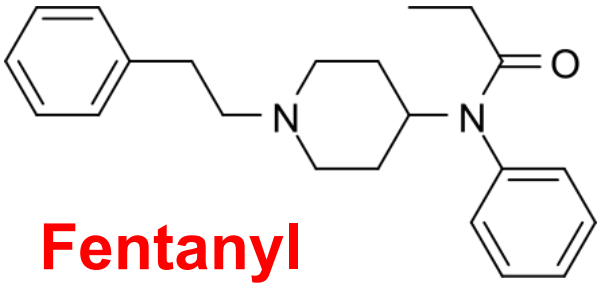
- Within the past 3 years, I have received research funding and/or study medications from Alkermes, BioXcel, Corbus, GoMedical (NIDA grant), Intra-cellular Therapies (NIDA grant), Janssen, and Lyndra (NIDA grant)

- I have also consulted for Alkermes, Mallinckrodt, and Opiant

Goals

- Current public health impact of fentanyl
- Pharmacology of fentanyl
- Impact on treatment of opioid use disorder (OUD)
  - Preclinical data
  - Early clinical data
- Possible solutions

What is fentanyl?



Fentanyl

- ✓ Potent synthetic opioid that is currently approved by the FDA
- ✓ First used medically in the 1960's as a general anesthetic
- ✓ Now used as a transdermal patch, lollipop, dissolving tablet and nasal spray for management of chronic or breakthrough pain

But Pharmaceutical Fentanyl is Not Driving the Current Epidemic

(Volkow, NIDA Council, May 2017)

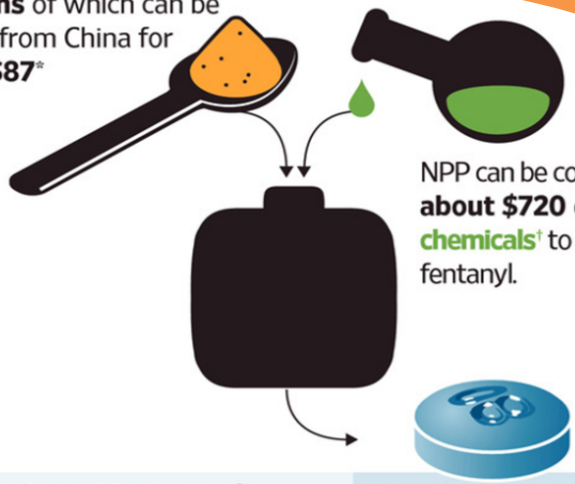
Fentanyl Synthesis from NPP

- **Large profit margin**
- **Easy to synthesize**
- **Easy to transport**

Criminal Chemistry

Traffickers manufacturing fentanyl often purchase the key ingredient from China, which doesn't regulate its sale. Here's how the chemical building blocks become a highly profitable street drug.

The key ingredient is NPP, 25 grams of which can be bought from China for **about $87***



NPP can be combined with **about $720** of other chemicals† to produce fentanyl.

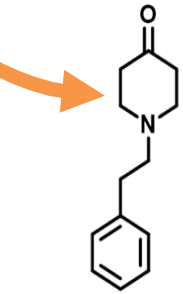
The resulting 25 grams of fentanyl cost about $810 to produce...

...and are equivalent to up to $800,000 of pills on the black market.

*Average current price from Chinese suppliers †Prices from U.S. suppliers

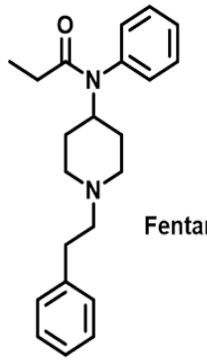
Sources: NES Inc.; Drug Enforcement Administration; Calgary Police

THE WALL STREET JOURNAL.



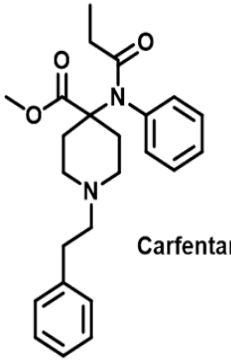
NPP
N-Phenethyl-4-piperidone

1. Reductive Amination w/ Aniline
2. Acylation w/ Propanoyl Chloride



Fentanyl

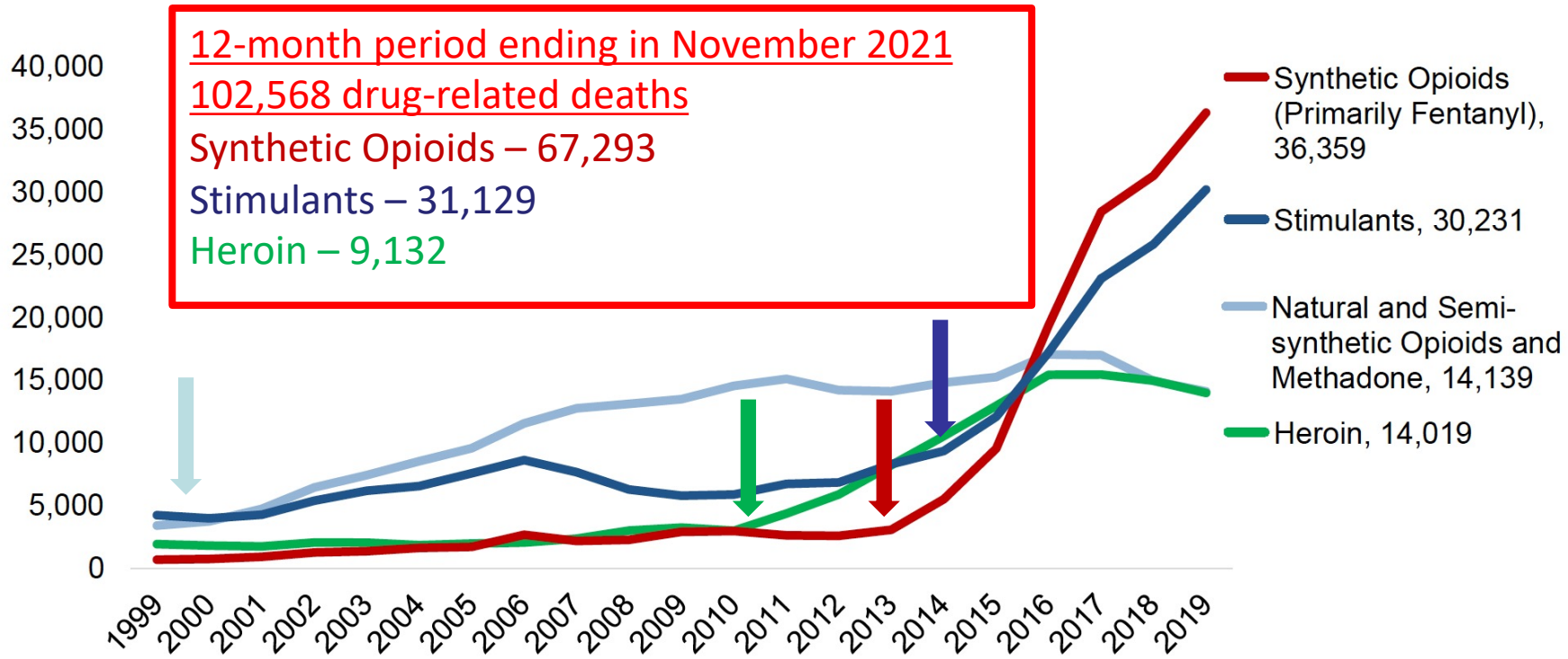
1. Potassium Cyanide, Aniline, Acid
2. Methanol, Acid
3. Propanoyl Chloride



Carfentanil

Evolution of Drivers of Overdose Deaths, All Ages

Analgesics → Heroin → Fentanyl → Stimulants



Source: The Multiple Cause of Death data are produced by the Division of Vital Statistics, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), United States Department of Health and Human Services (US DHHS).

Increased Overdose Death Rates During COVID-19 Pandemic

12-months Ending July 2020 Compared to 12-months Ending July 2019

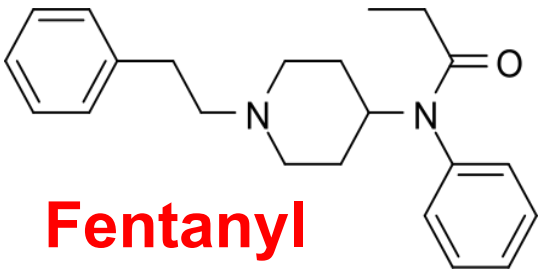
	ALL DRUGS	HEROIN	NAT & SEMI – SYNTHETIC	METHADONE	SYNTHETIC OPIOIDS	COCAINE	OTHER PSYCHO-STIMULANTS (mainly meth)
July 2019 *		14,793	12,203	2,875	33,704	15,031	14,941
March 2020*	75,687	14,145	12,349	2,837	40,756	17,465	18,033
July 2020*	86,001	14,427	13,259	3,315	50,122	19,542	20,406
July 2019-July 2020 Change	**+24.2%**	**-2.5%**	**+8.7%**	**+15.3%**	**+48.7%**	**+30.0%**	**+36.6%**

NIH National Institute on Drug Abuse
Advancing Addiction Science

*NCHS Provisional Drug Overdose Death Counts: *https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm*

(Volkow, 2021)

Why are the fentanyls driving the rates of fatal overdoses?



Fentanyl

Lethal Doses of Heroin and Fentanyl

- ✓ ~100x more potent than morphine (50x more potent than heroin)

Received: 28 February 2021 | Revised: 27 April 2021 | Accepted: 12 May 2021

DOI: 10.1111/bph.15573

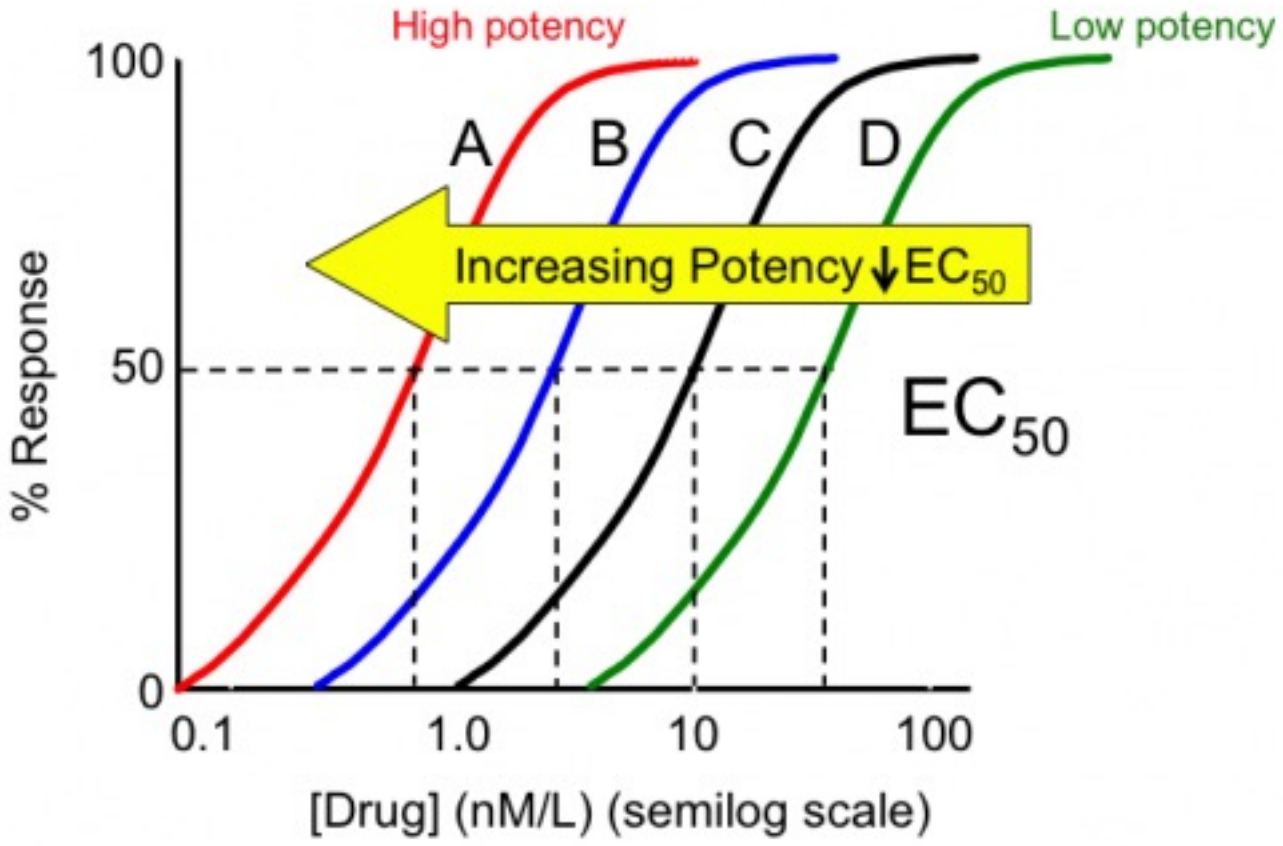
REVIEW ARTICLE

BJP BRITISH PHARMACOLOGICAL SOCIETY

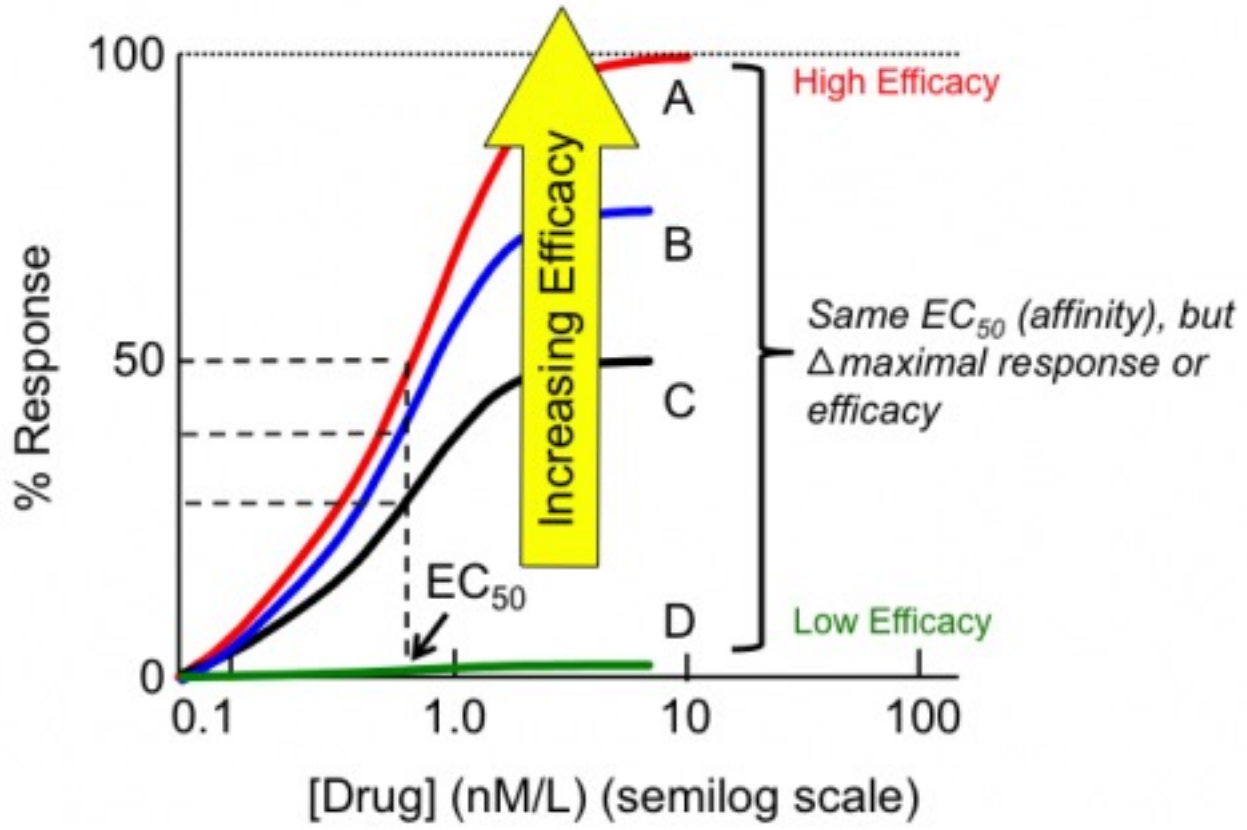
The anomalous pharmacology of fentanyl

Eamonn Kelly | Katy Sutcliffe | Damiana Cavallo | Nokomis Ramos-Gonzalez | Norah Alhosan | Graeme Henderson

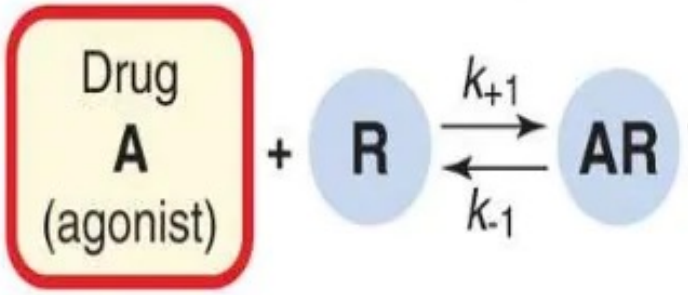
POTENCY


High potency
Low potency
100
50
0
A
B
C
D
Increasing Potency ↓ EC50
EC50
% Response
0.1
1.0
10
100
[Drug] (nM/L) (semilog scale)

EFFICACY

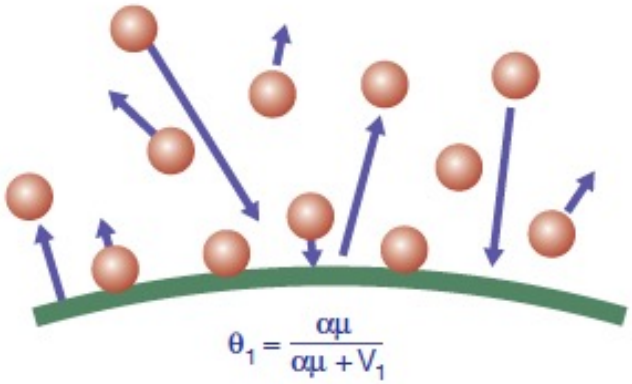

100
50
0
% Response
0.1
1.0
10
100
[Drug] (nM/L) (semilog scale)
Increasing Efficacy
A
B
C
D
EC50
High Efficacy
Low Efficacy
Same EC50 (affinity), but
Δmaximal response or
efficacy

AFFINITY

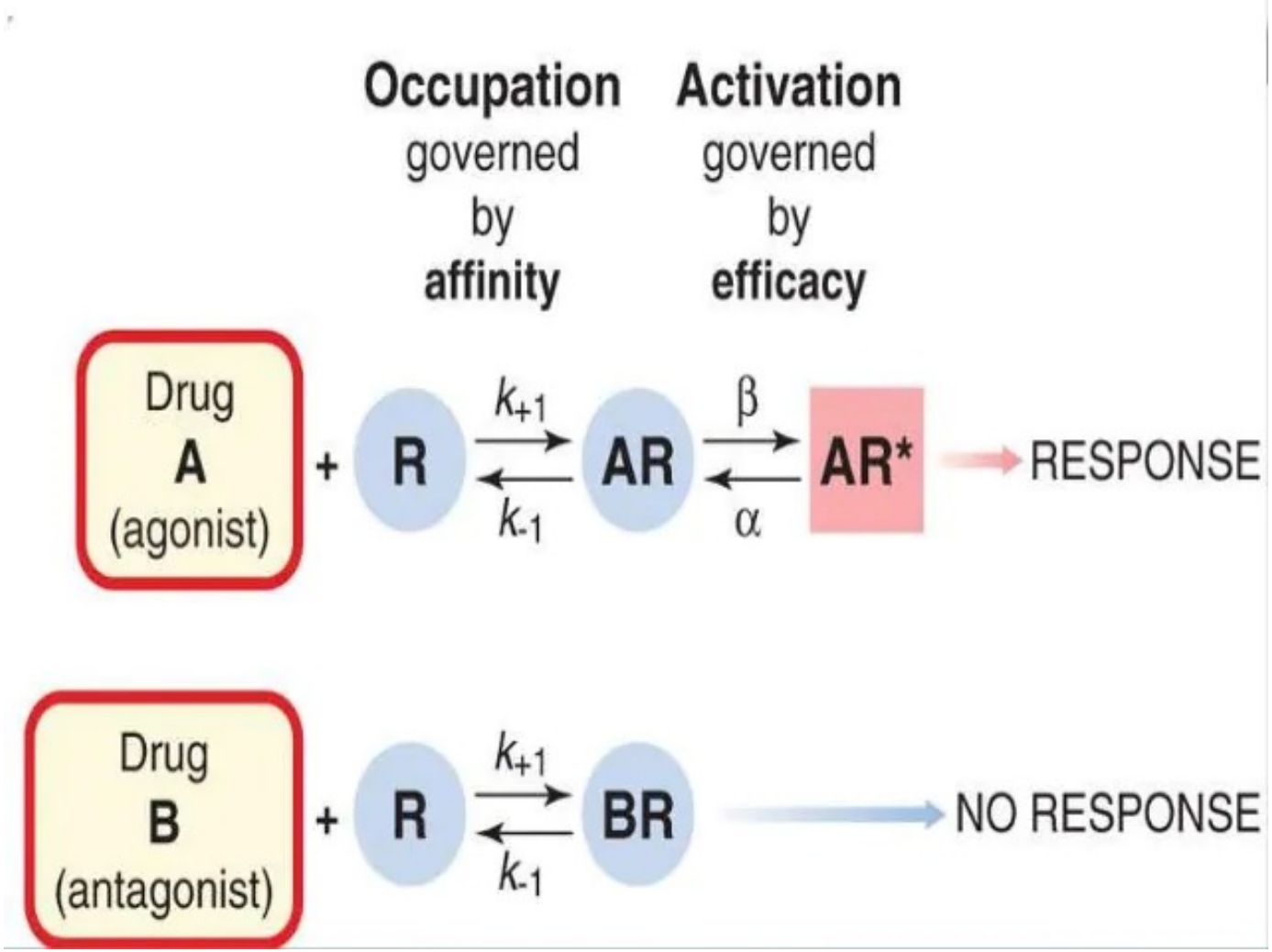


K_d = dissociation constant (k_{off}/k_{on})

FIGURE 1.9 The Langmuir adsorption isotherm representing the binding of a molecule to a surface. Photo shows Irving Langmuir (1881–1957), a chemist interested in the adsorption of molecules to metal filaments for the production of light. Langmuir devised the simple equation still in use today for quantifying the binding of molecules to surfaces. The equilibrium is described by condensation and evaporation to yield the fraction of surface bound (θ_1) by a concentration μ.



AFFINITY vs EFFICACY



Kelly et al 2021: AFFINITY (radioligand binding studies)
fentanyl ~ morphine

TABLE 1C Comparison of fentanyl and morphine in *in vitro* and *in vivo* assay systems: Radioligand binding (membrane homogenates)

	Species of μ receptor (tissue)	Fentanyl (K_i, nM)	Morphine (K_i, nM)	Relative affinity of fentanyl:morphine	Reference
High Na^+ (100–137 mM)	Rat	158	250	1.6-fold	McPherson et al. (2010)
	Rat	157	132	0.8-fold	Emmerson et al. (1996)
	Guinea pig (brain)	162	177	1.1-fold	Kosterlitz and Leslie (1978)
	Human	2.8[a]	6.4[a]	2.2-fold	Schmid et al. (2017)
Zero Na^+	Human	1.6	4.0	2.6-fold	Hassanien et al. (2020)
	Human	0.5	0.8	1.6-fold	Heusler et al. (2015)
	Rat	0.135	0.252	1.9-fold	Eshleman et al. (2020)
	Rat	0.35	0.58	1.7-fold	Torralva et al. (2020)
	Rat	0.16	0.16	1.0-fold	Emmerson et al. (1996)
	Guinea pig (brain)	4.2	2.7	0.6-fold	Kosterlitz and Leslie (1978)

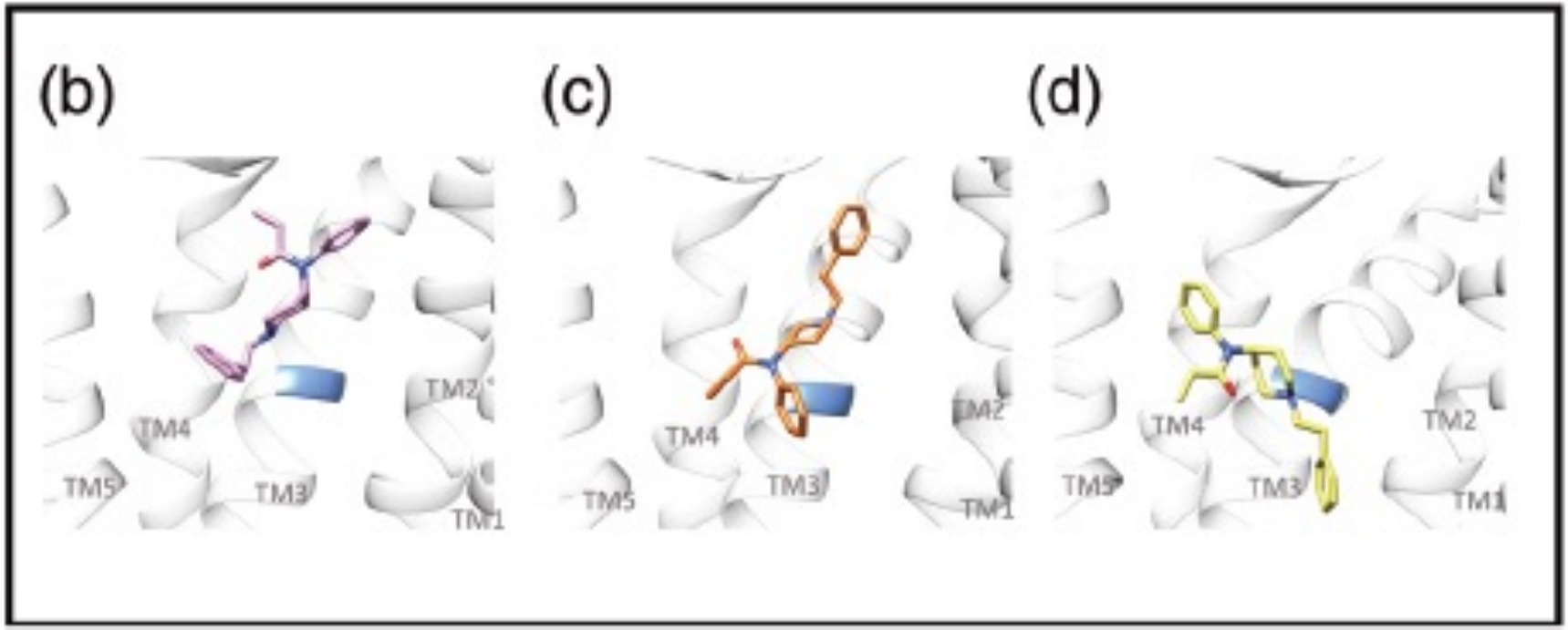
[a]In this study by Schmid et al., the authors state that the assay was performed in the presence of Na (100 mM), but the high affinity for both ligands (low nM values) would indicate the absence of Na. Either way it does not matter as the ratio is close to 1.

Kelly et al 2021: POTENCY & EFFICACY ([^{35}S]GTPγS binding)
fentanyl 0.6-5.2x as potent as morphine
(or 13.9x using cell-based assays)
fentanyl and morphine have similar efficacy

TABLE 1D Comparison of fentanyl and morphine in *in vitro* and *in vivo* assay systems: Stimulation of [^{35}S]GTPγS binding (membrane homogenates)

Species of μ receptor	Fentanyl EC_{50} (nM)	Morphine EC_{50} (nM)	Relative potency of fentanyl:morphine	E_{max} (relative efficacy) of fentanyl:morphine (c.f. DAMGO 100)	Reference
Recombinant receptors					
Human	32	150	4.7-fold	89:98	Hassanien et al. (2020)
Human	43	64	1.5-fold	80:81	Schmid et al. (2017)
Human	2.6	3.6	1.4-fold	112:111	Heusler et al. (2015)
Human	27.8	125	4.5-fold	107:90	Obeng et al. (2021)
Human					Saidak et al. (2006)
Ga_{i1}	119	213	1.8-fold	69:66	
Ga_{oA}	67	89	1.3-fold	72:88	
Rat	21.4	26.1	1.2-fold	89:82	Eshleman et al. (2020)
Rat	18	38	2.1-fold	92:86	Torralva et al. (2020)
Rat	56.8	97.5	1.7-fold	110:94	McPherson et al. (2010)
Rat	58	73	1.3-fold	86:74	Clark et al. (2006)
Rat	–	28.3	–	97:83	Emmerson et al. (1996)
Mouse	59.7	36.3	0.6-fold	–	Zaki et al. (2000)
Mouse	23	120	5.2-fold	110:106	Selley et al. (1997)
Native tissue (species)					
SK-N-SH cells (human)	37.5	138	3.7-fold	66:73	Selley et al. (1997)
SH-SY-5Y cells (human)	15.2	26.7	1.8-fold	91:75	Traynor and Nahorski (1995)
Spinal cord (mouse)	135	407	3.0-fold	83:78	Madia et al. (2012)
Thalamus (rat)	117	434	3.7-fold	58:56	Selley et al. (1997)

Kelly et al 2021: Fentanyl may interact with the orthosteric binding pocket of MORs in multiple ways



Kelly et al 2021: Fentanyl may have multiple binding pathways

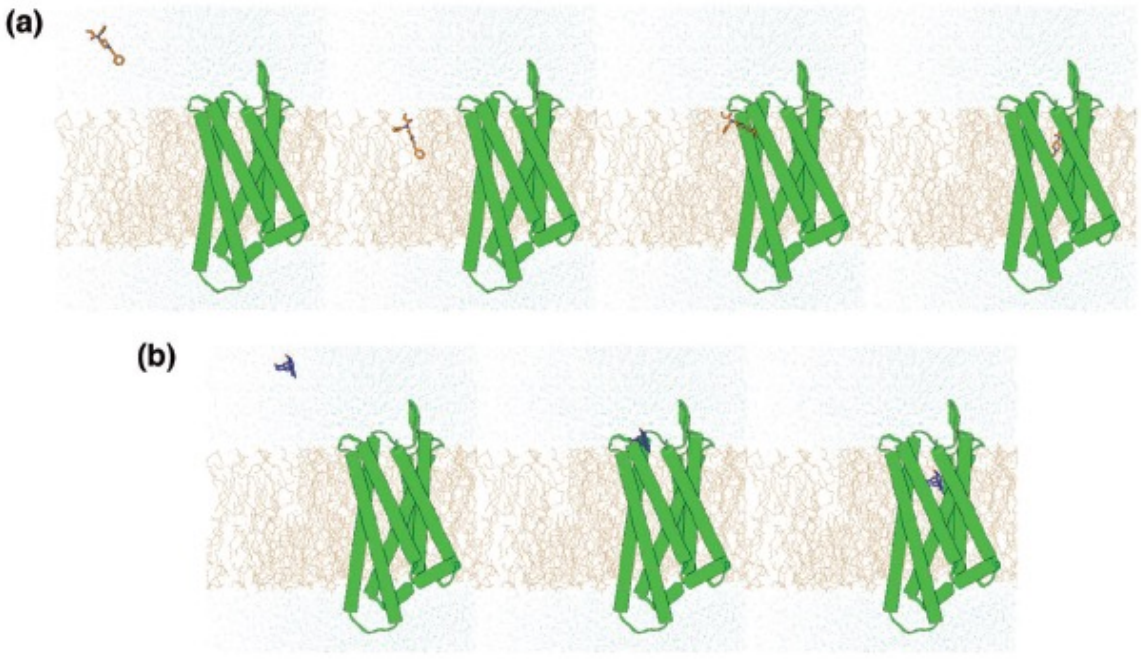


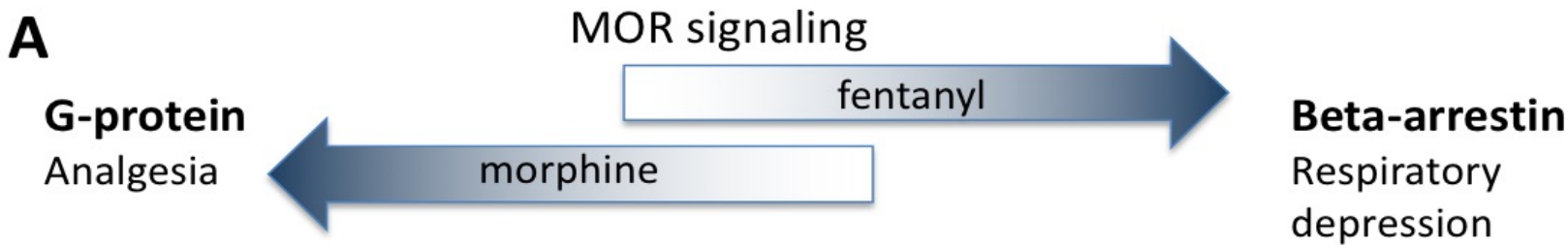
FIGURE 3 The lipid binding pathway for fentanyl identified by coarse-grained molecular dynamics simulations. (a) A molecule of fentanyl approaches and then enters the lipid membrane, before entering the μ receptor through a pore between transmembrane domains 6 and 7 of the receptor and eventually entering the orthosteric binding pocket. (b) A molecule of morphine approaches and then enters the μ receptor from above the receptor (the aqueous route)

Kelly et al 2021: CROSS-TOLERANCE

In morphine-dependent animals, cross-tolerance to morphine is greater than cross-tolerance to fentanyl

Fentanyl does not produce tolerance as readily as morphine

How does fentanyl differ from heroin (morphine)?



Morphine	Fentanyl
Little to no MOR internalization	MOR internalization
beta-arrestin 2 KO mice No analgesic tolerance No locomotor sensitization Tolerance JNK-dependent	beta-arrestin-2 KO mice Tolerance not affected Locomotor sensitization not changed Tolerance JNK-independent
Tolerance is GRK3-independent	Tolerance is GRK3-dependent
RGS9-2 KO *increases* analgesia	RGS9-2 KO *decreases* analgesia
No ERK1/2 activation (via b-arrestin-2)	ERK1/2 activation (via b-arrestin-2)
Potency = 1	Potency = 0.01 morphine equivalent
Less lipophilic	More lipophilic
Slow CNS entry	Rapid CNS entry

Comer and Cahill (2019)

FDA-approved medications for treating OUD

- ✓ Maintenance medications
  - Methadone (full mu agonist)
  - Buprenorphine (partial mu agonist)
  - Naltrexone (antagonist)
- ✓ Overdose reversal
  - Naloxone (antagonist)
  - Nalmefene (antagonist)

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Methods

Comer et al (1992) J Pharmacol Exp Ther 262(3): 1051-1056

Species: Mice

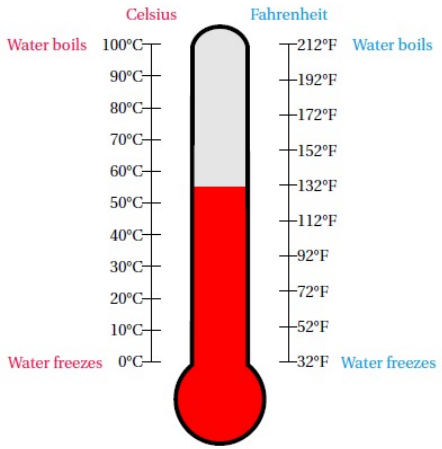
Assay: Warm water (55ºC) tail withdrawal

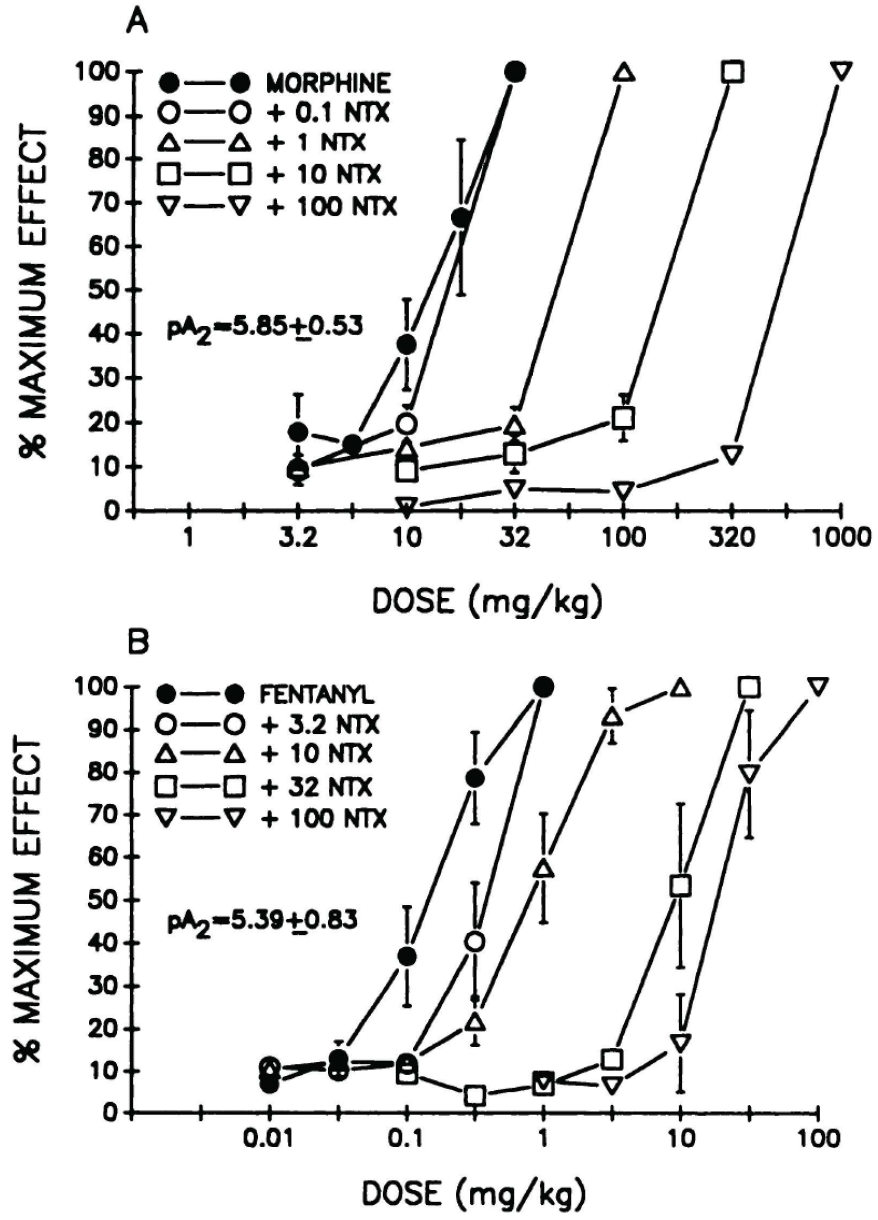
Dependent measure: Latency to withdrawal

$$\% \text{ Maximum possible effect} = \frac{\text{Test latency - Control latency}}{\text{15 sec - Control latency}} \times 100$$

Antagonists: Naltrexone or C-CAM

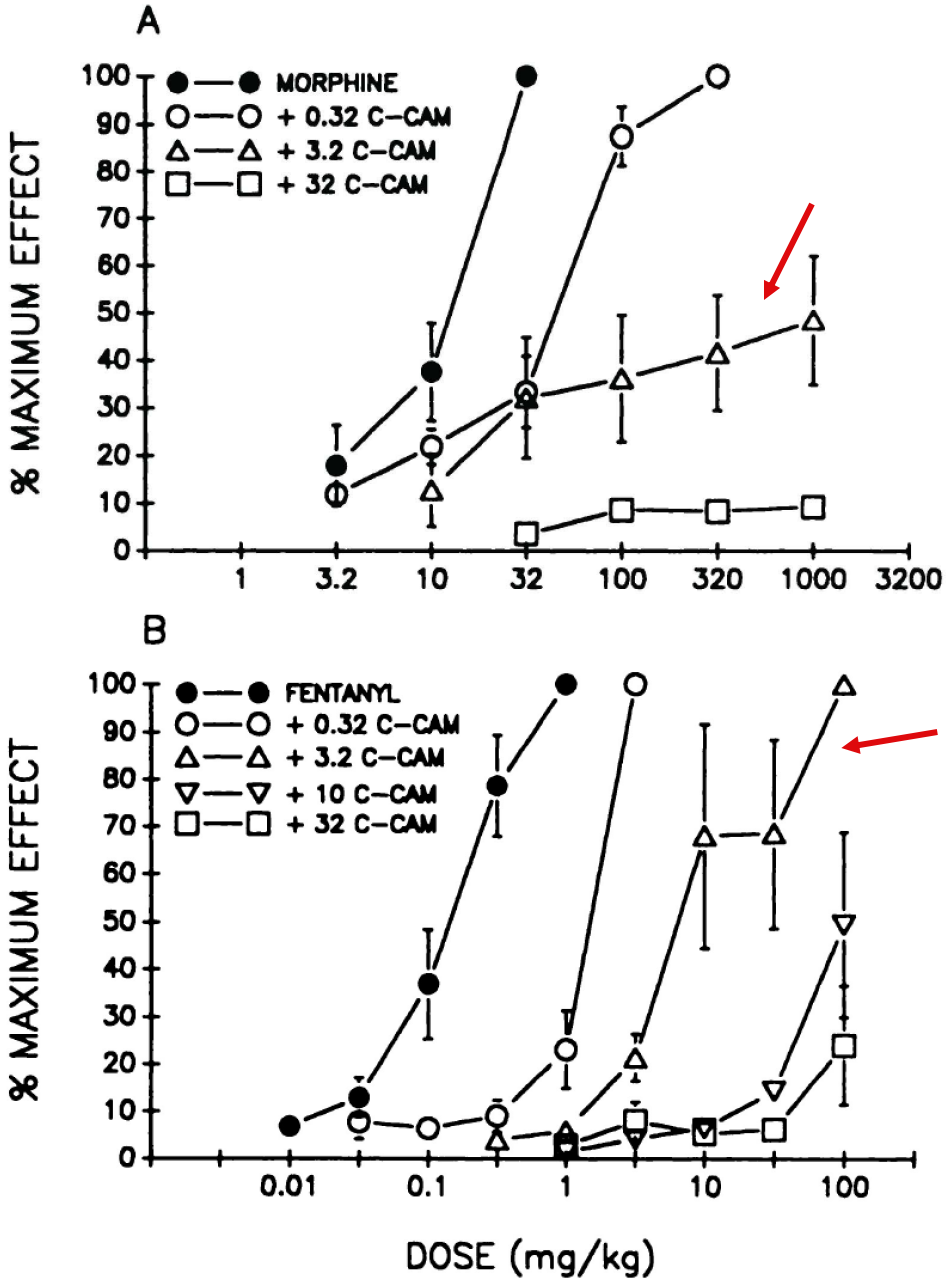
Test drugs: Morphine, fentanyl





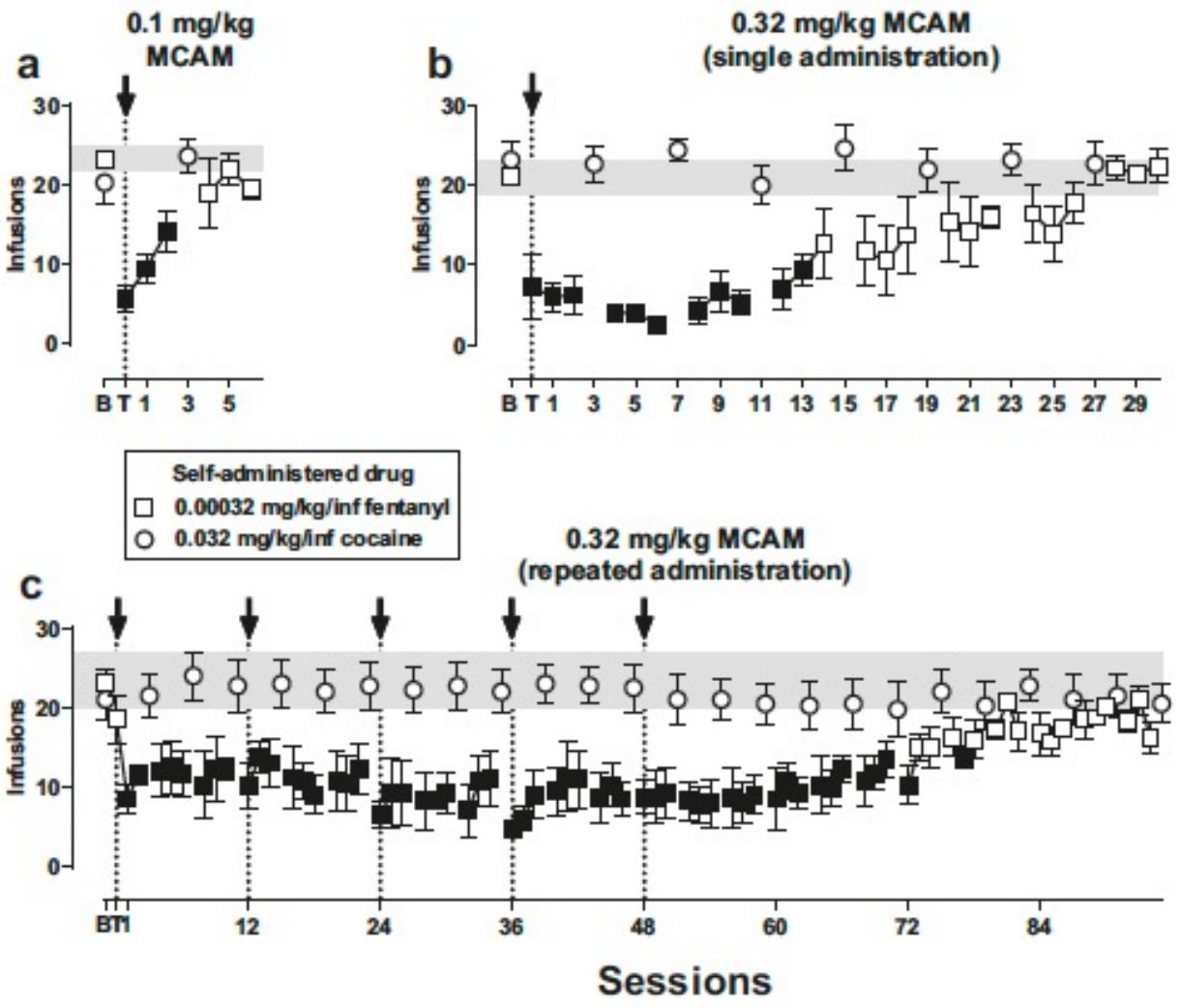
The potency of naltrexone against morphine and fentanyl was the same, suggesting that they were producing their effects through the same receptors (μ).

Comer et al (1992) J Pharmacol Exp Ther 262(3): 1051-1056



However, higher doses of an irreversible antagonist were needed to produce downward shifts in the dose-effect curve for fentanyl compared to morphine.

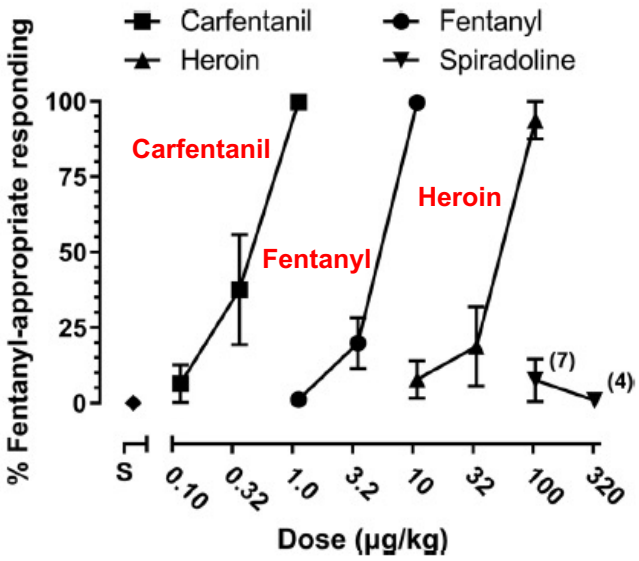
Comer et al (1992) J Pharmacol Exp Ther 262(3): 1051-1056



MCAM, a pseudoirreversible antagonist, produced a long-lasting reduction in fentanyl self-administration in rhesus monkeys.

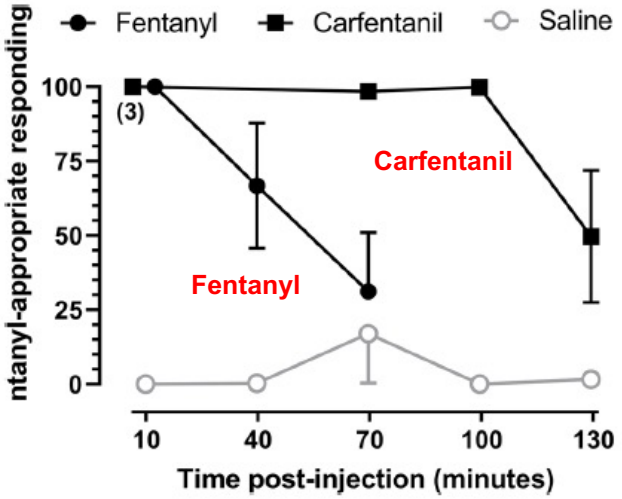
Maguire et al (2020) Neuropsychopharmacol 45: 1986-1993

THE ANTAGONIST IS IMPORTANT – COMPETITIVE VS NON-COMPETITIVE INTERACTIONS



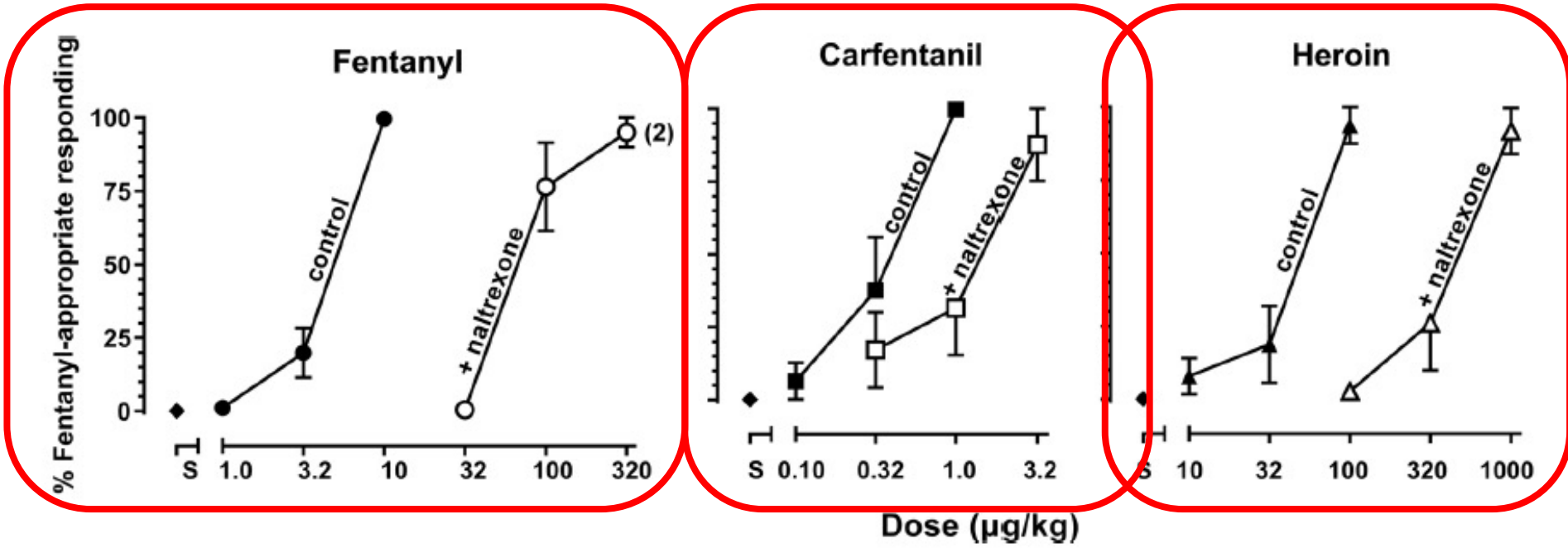
Fentanyl and carfentanil produce effects that are similar to heroin in rats.

But carfentanil produces longer lasting effects than fentanyl.



Flynn and France (2021) Drug and Alcohol Dependence 221: 108599

Although naltrexone antagonizes fentanyl and heroin to a similar extent, it is less effective against carfentanil.



Flynn and France (2021) Drug and Alcohol Dependence 221: 108599

THE AGONIST IS IMPORTANT TOO – FENTANYL VS CARFENTANIL

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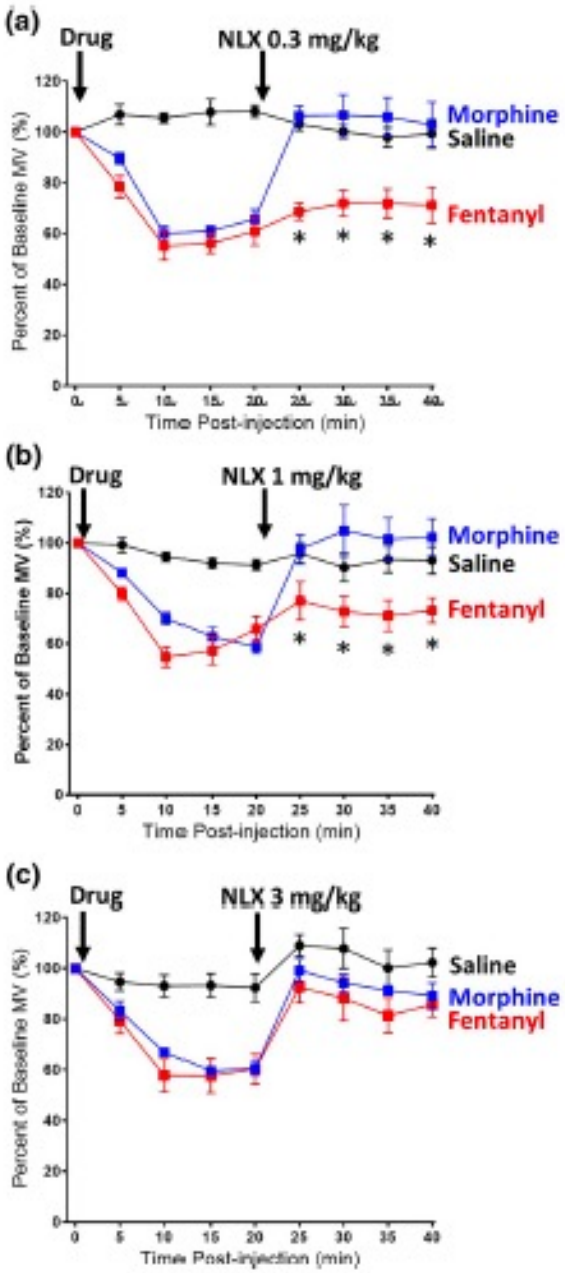

FIGURE 4 A higher concentration of naloxone is required to reverse respiratory depression by fentanyl than by morphine. Data are from Hill et al. (2020) in which respiration was monitored in freely moving mice by plethysmography and drugs injected intraperitoneally

Kelly et al 2021: NALOXONE REVERSAL – 10X HIGHER DOSES NEEDED FOR FENTANYL

CASE REPORT

Higher naloxone dosing may be required for opioid overdose

Russell Bardsley, Pharm.D., BCPS, BCCCP, Emergency Department, Catholic Medical Center, Manchester, NH.

AM J HEALTH-SYST PHARM | VOLUME 76 | NUMBER 22 | NOVEMBER 15, 2019

Moss and Carlo *Substance Abuse Treatment, Prevention, and Policy* (2019) 14:6
https://doi.org/10.1186/s13011-019-0195-4

Substance Abuse Treatment, Prevention, and Policy

DEBATE Open Access

Higher doses of naloxone are needed in the synthetic opioid era

Ronald B. Moss* and Dennis J. Carlo

bidity and Mortality Weekly Report

Characteristics of Fentanyl Overdose — Massachusetts, 2014–2016

Nicholas J. Somerville, MD[1,2]; Julie O'Donnell, PhD[1,3]; R. Matthew Gladden, PhD[4]; Jon E. Zibbell, PhD[4]; Traci C. Green, PhD[5]; Morgan Younkin, MD[6]; Sarah Ruiz, MSW[2]; Hermik Babakhanlou-Chase, MPH[2]; Miranda Chan, MPH[2]; Barry P. Callis, MSW[2]; Janet Kuramoto-Crawford, PhD[1]; Henry M. Nields, MD, PhD[7]; Alexander Y. Walley, MD[2,5]

Can J Anesth/J Can Anesth (2019) 66:414–421
https://doi.org/10.1007/s12630-019-01294-y

MMWR / April 14, 2017 / Vol. 66 / No. 14 US Department of Health and Human Services/Centers for Disease Control and Prevention

REVIEW ARTICLE/BRIEF REVIEW

Carfentanil: a narrative review of its pharmacology and public health concerns

Carfentanil: étude narrative de sa pharmacologie et problématiques de santé publique

Jessica L. S. Leen, MD · David N. Juurlink, MD, PhD

1521-0103/371/2/453–475$35.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

https://doi.org/10.1124/jpet.119.258566
J Pharmacol Exp Ther 371:453–475, November 2019

Special Section on The Opioid Crisis

Noradrenergic Mechanisms in Fentanyl-Mediated Rapid Death Explain Failure of Naloxone in the Opioid Crisis

Randy Torralva and Aaron Janowsky

CODA Inc., Research Department, Portland, Oregon (R.T.); Research Service, VA Portland Health Care System, Portland, Oregon (R.T., A.J.); and Department of Psychiatry, Oregon Health & Science University, Portland, Oregon (R.T., A.J.)

Received April 2, 2019; accepted September 3, 2019

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Methods

Walker & Young Psychopharmacology (2001) 154: 131-142

Species: Rats

Assay: Warm water (55ºC) tail withdrawal

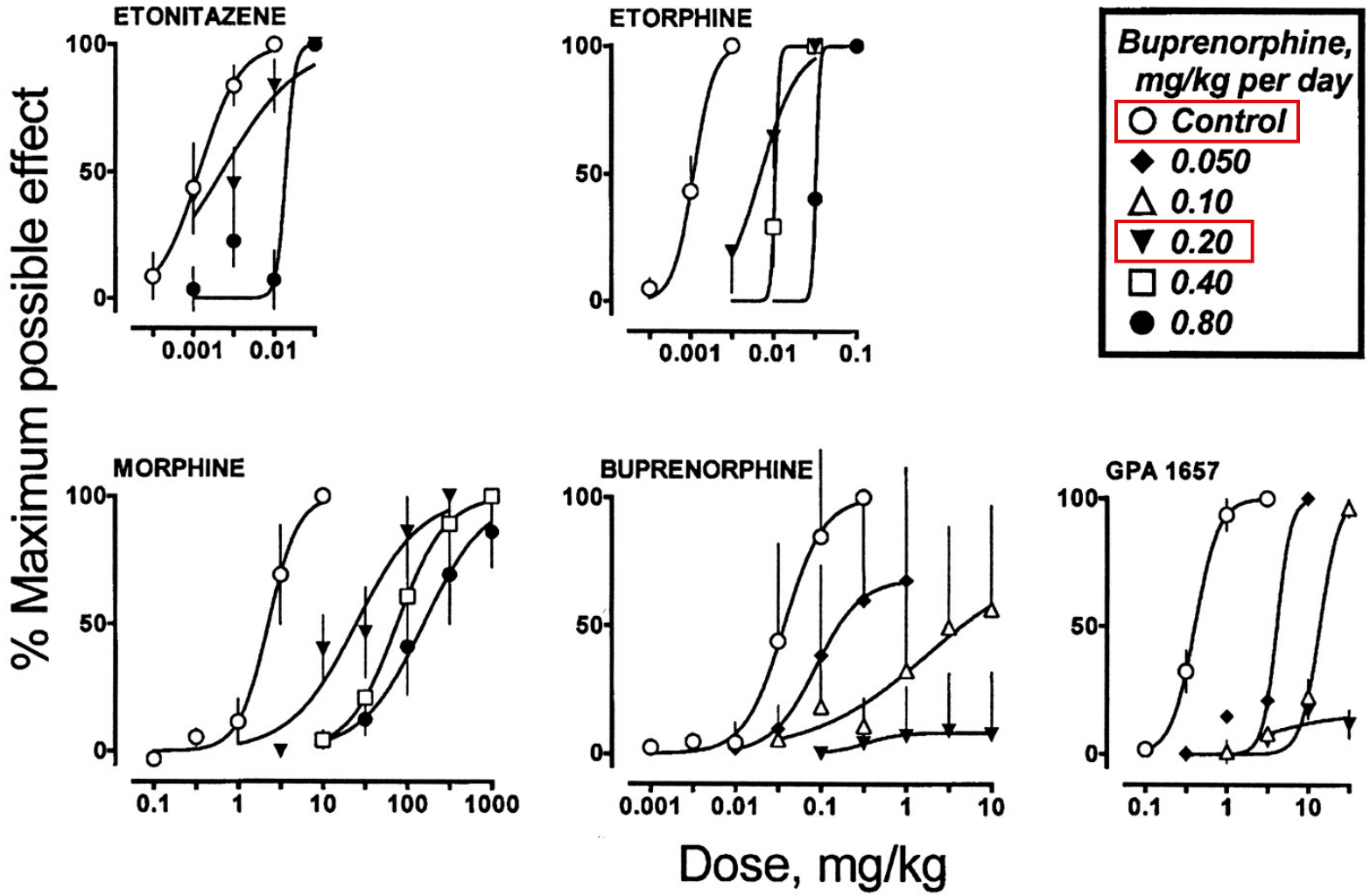
Dependent measure: Latency to withdrawal

$$\% \text{ Maximum possible effect} = \frac{\text{Test latency - Control latency}}{\text{15 sec - Control latency}} \times 100$$

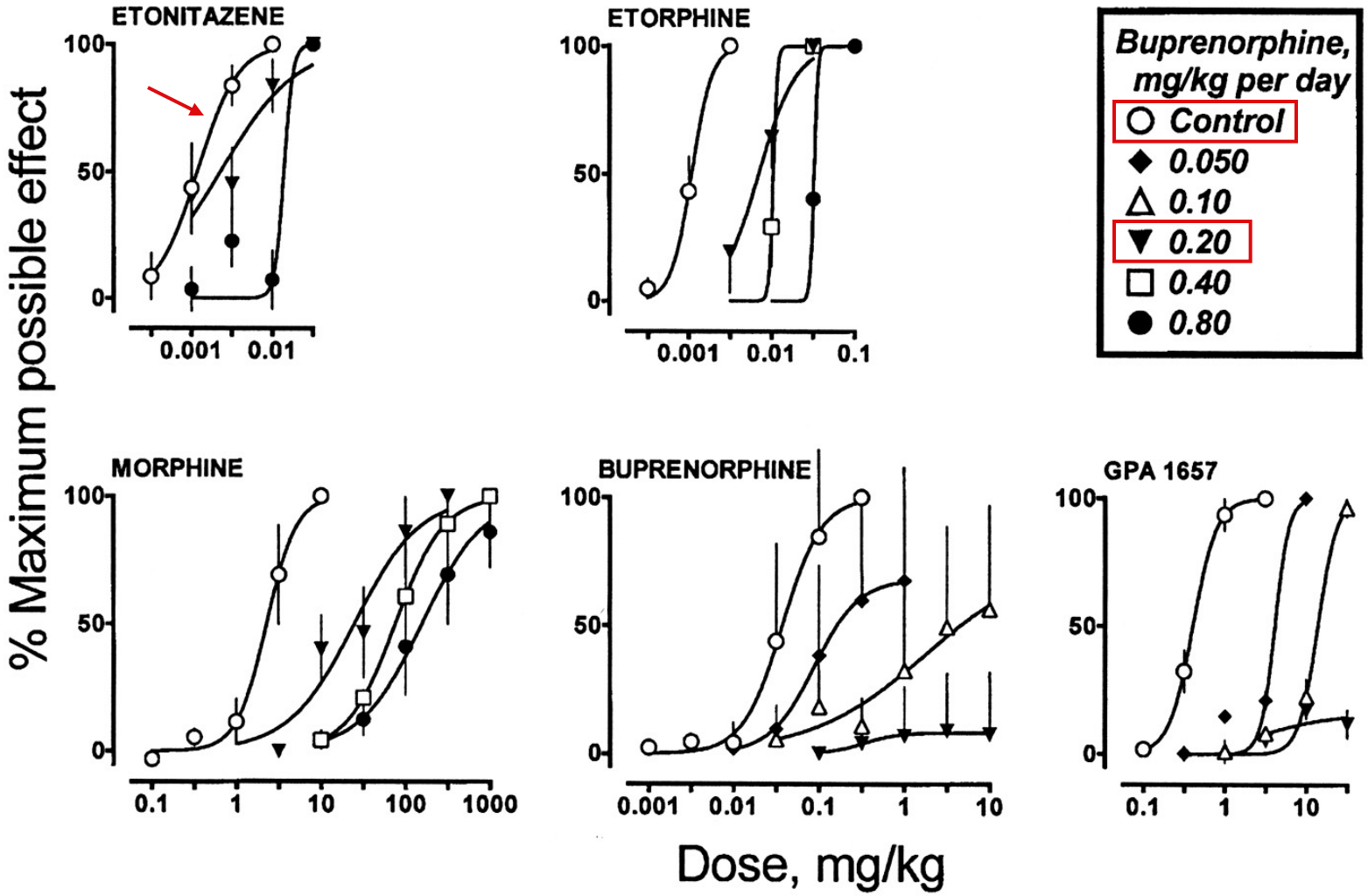
Maintenance drug: Buprenorphine

Test drugs: Etonitazene, etorphine, morphine, buprenorphine,

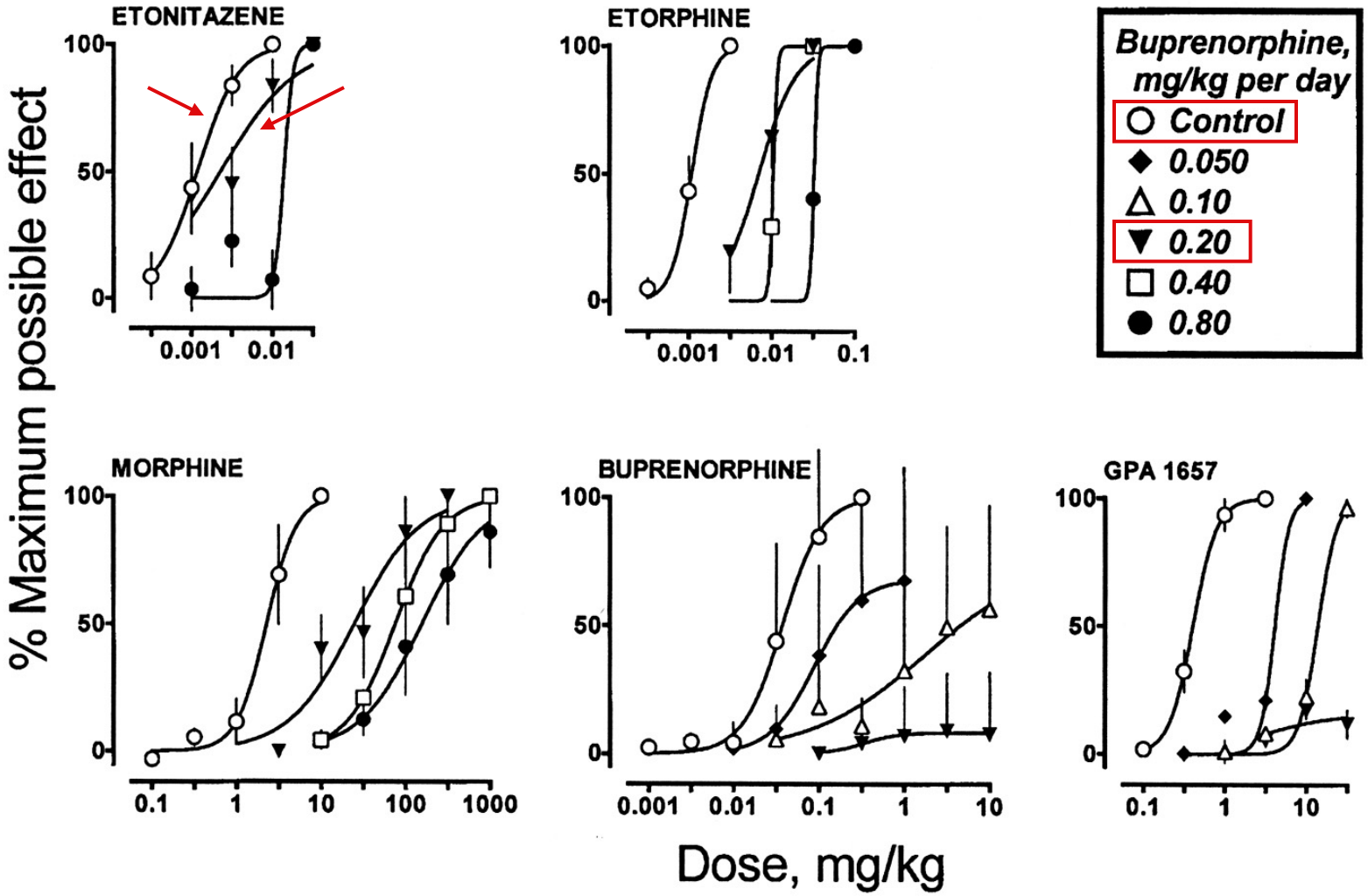
GPA 1657



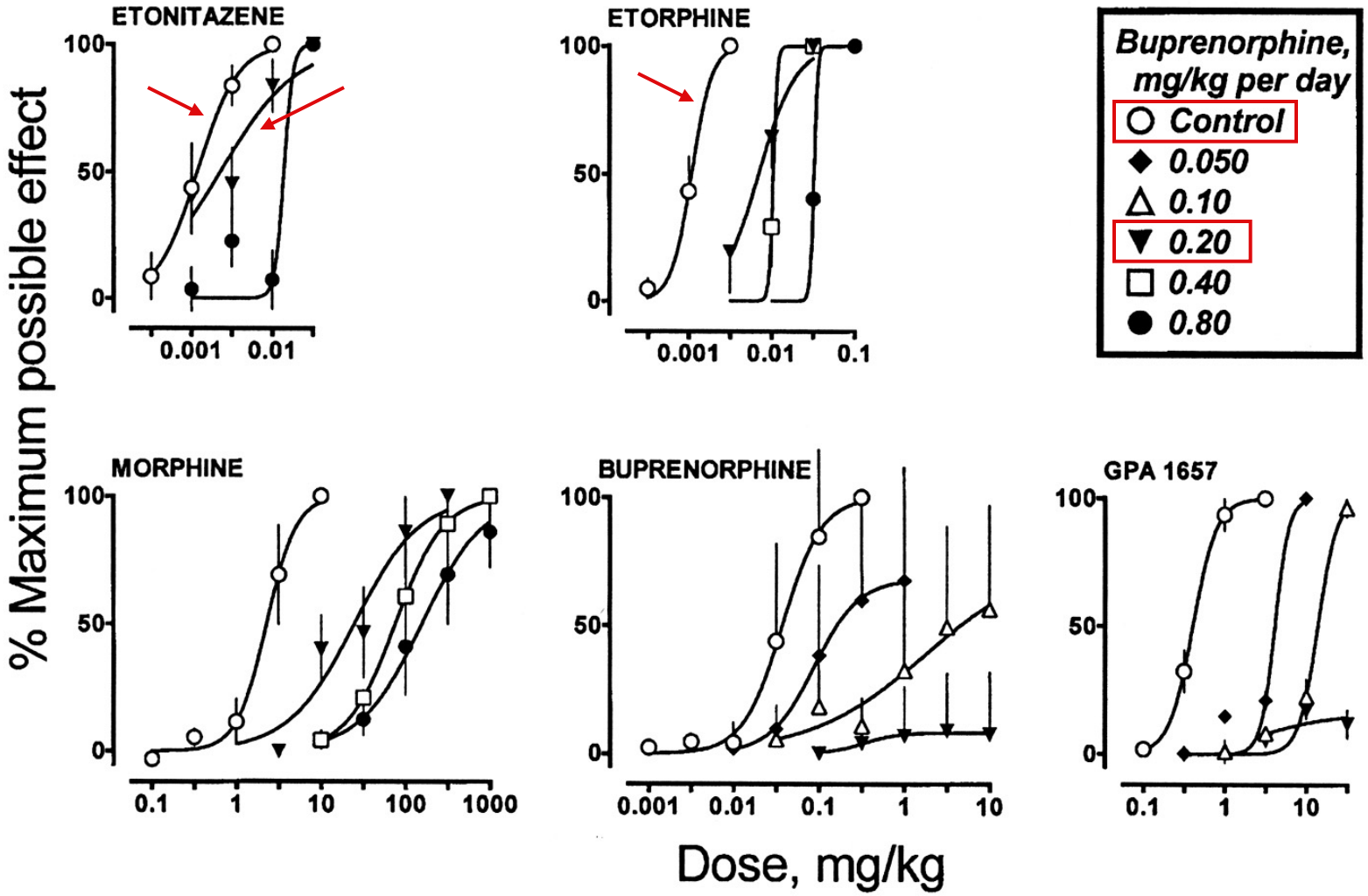
Walker & Young Psychopharmacology (2001) 154: 131-142



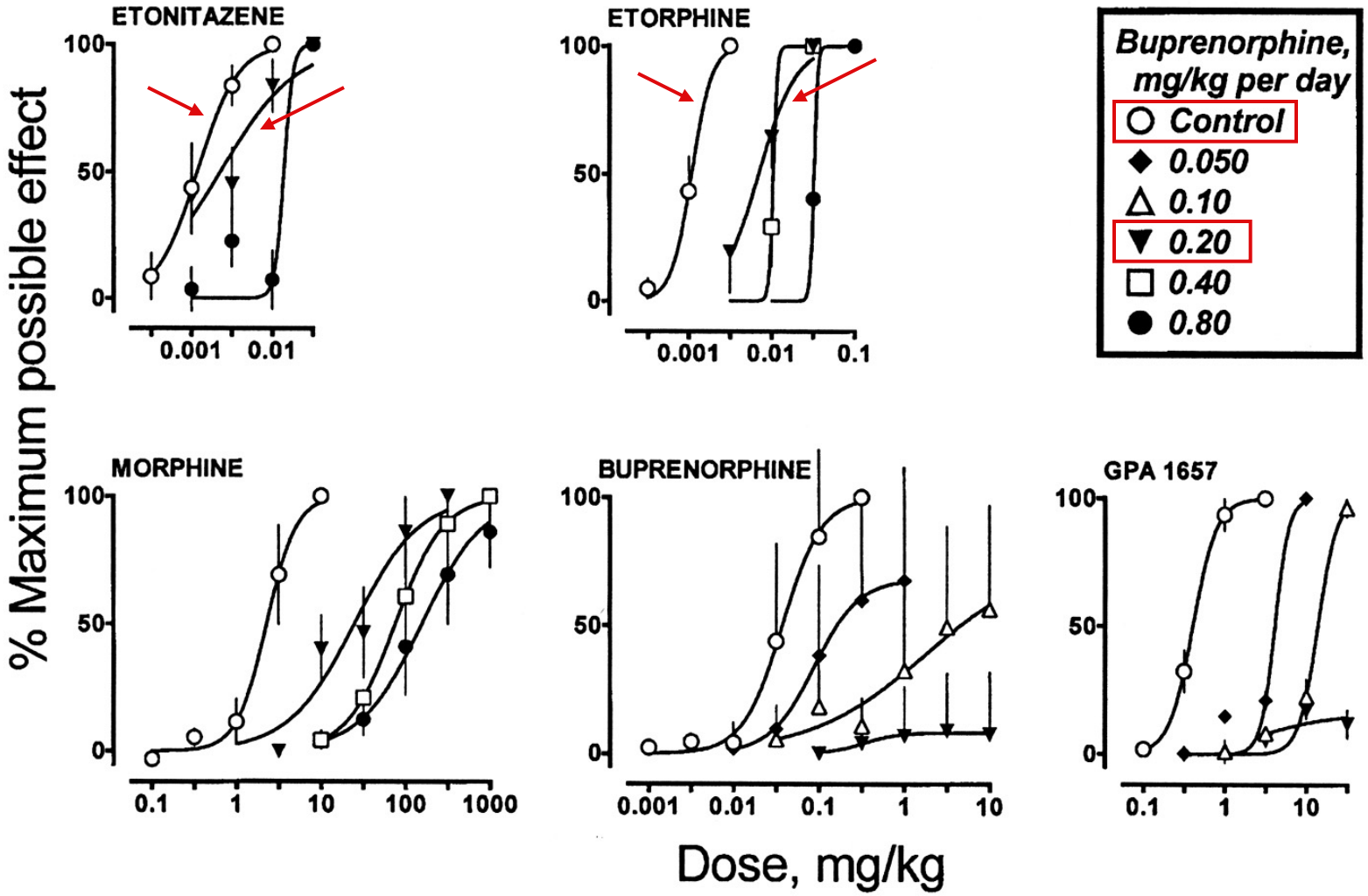
Walker & Young Psychopharmacology (2001) 154: 131-142



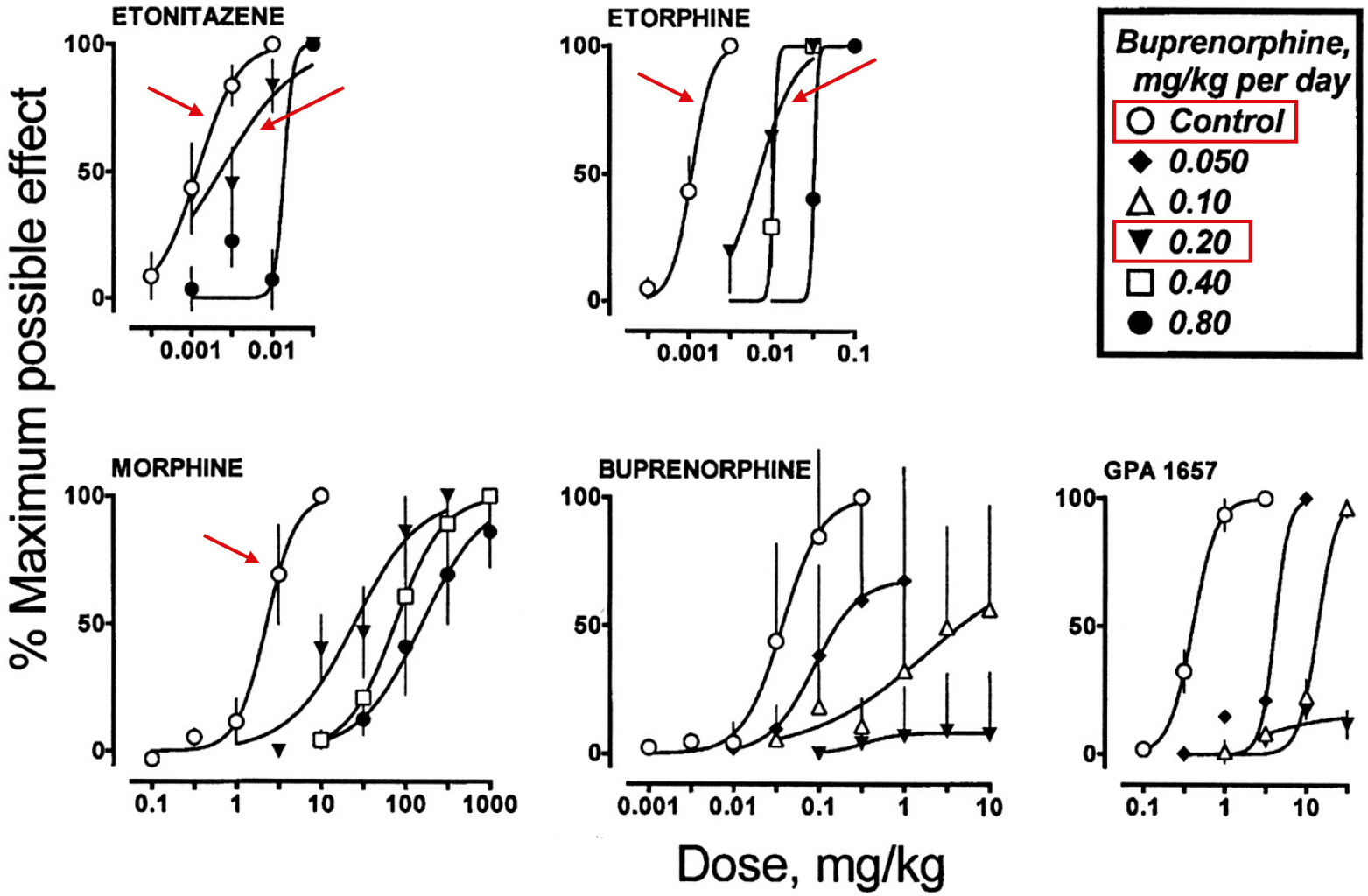
Walker & Young Psychopharmacology (2001) 154: 131-142



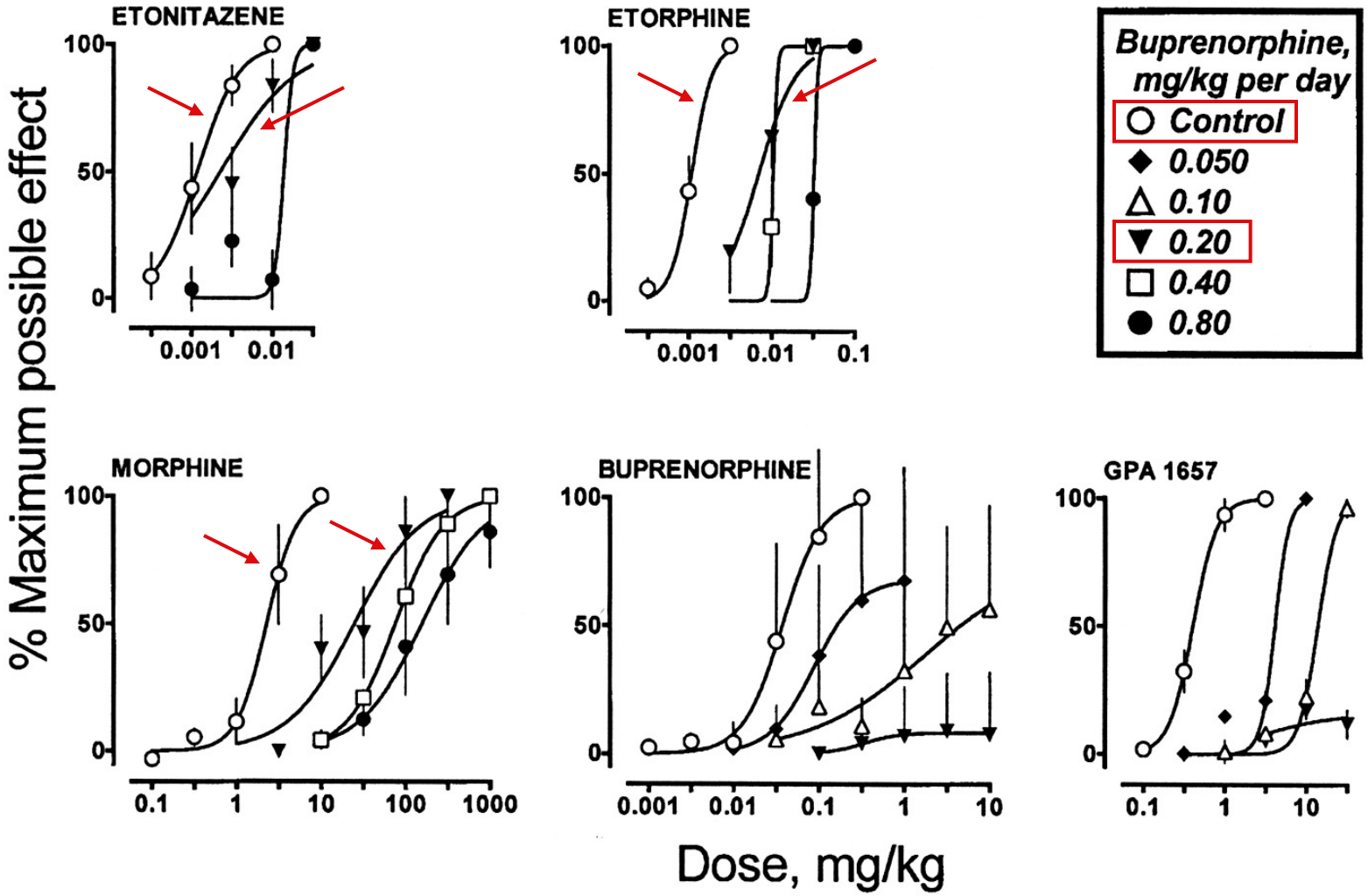
Walker & Young Psychopharmacology (2001) 154: 131-142



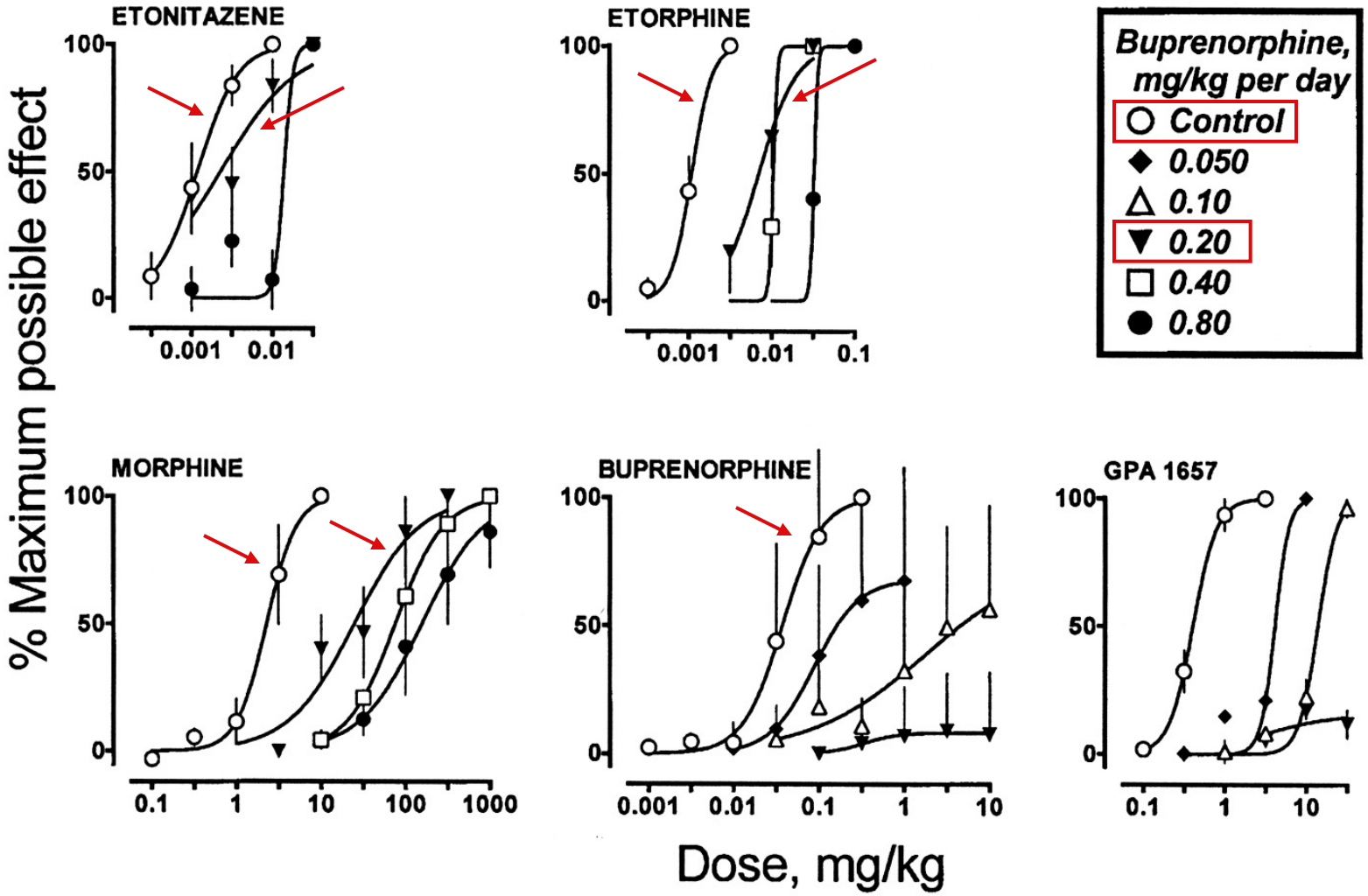
Walker & Young Psychopharmacology (2001) 154: 131-142



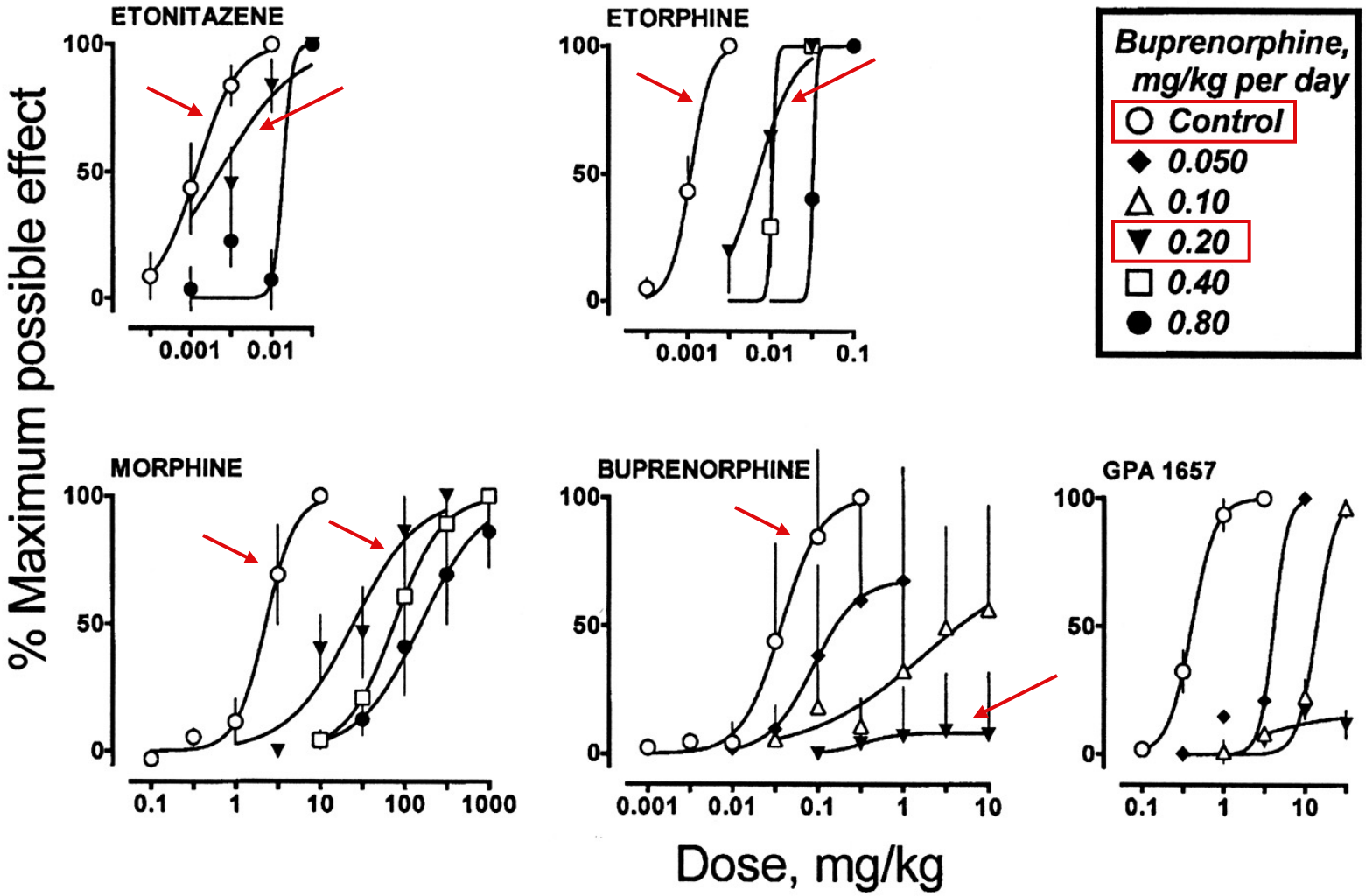
Walker & Young Psychopharmacology (2001) 154: 131-142



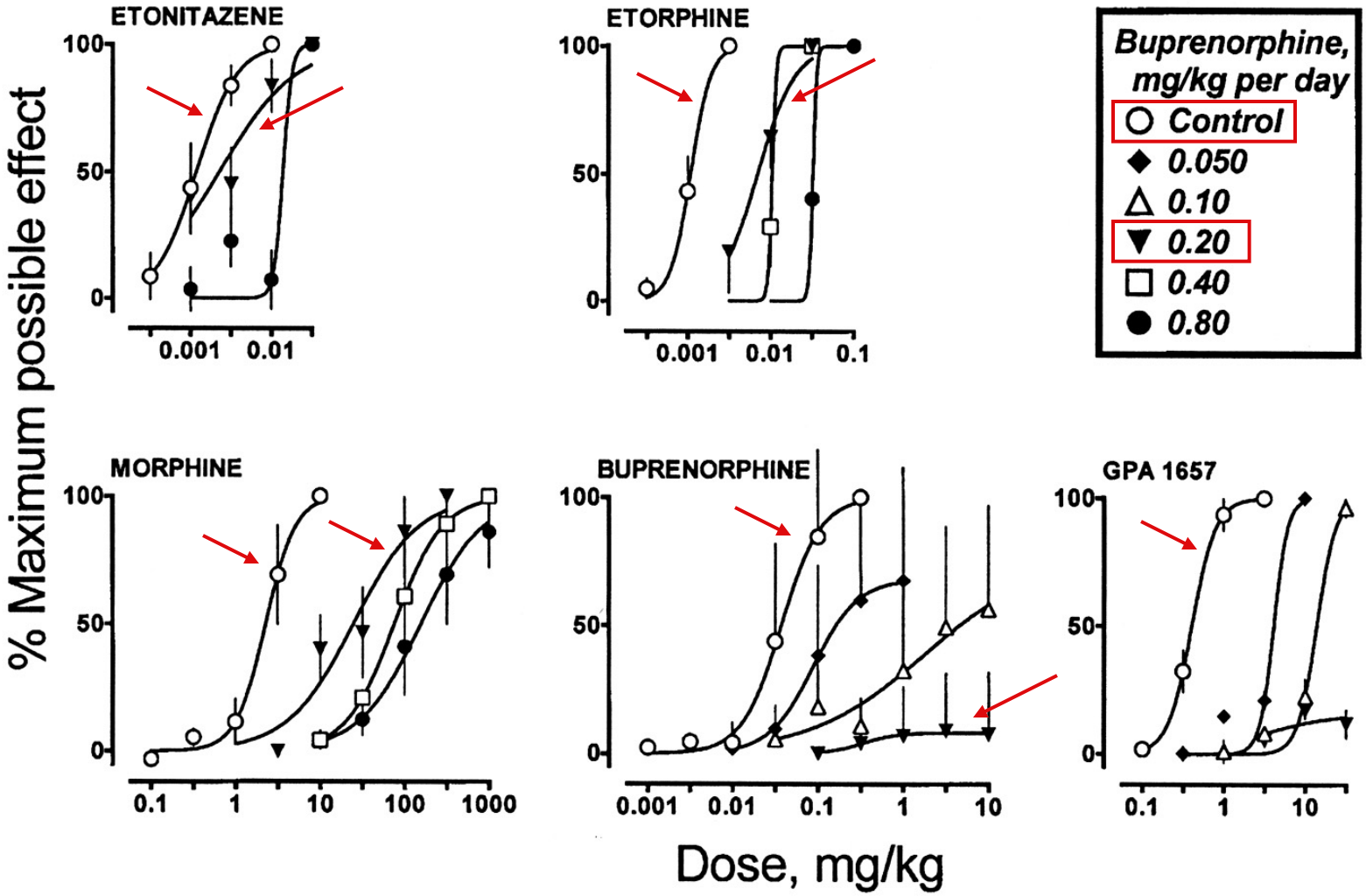
Walker & Young Psychopharmacology (2001) 154: 131-142



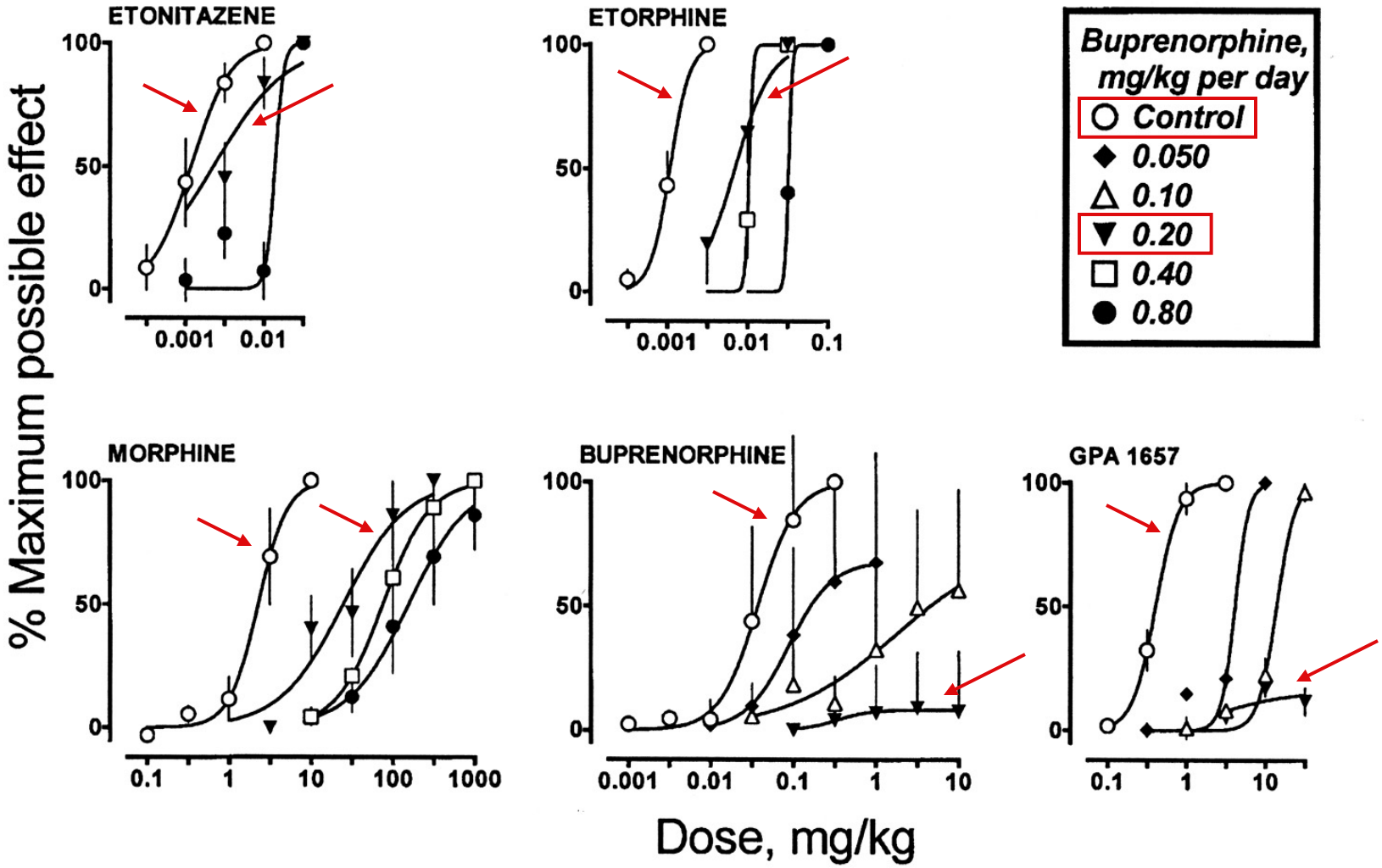
Walker & Young Psychopharmacology (2001) 154: 131-142



Walker & Young Psychopharmacology (2001) 154: 131-142



Walker & Young Psychopharmacology (2001) 154: 131-142



Walker & Young Psychopharmacology (2001) 154: 131-142

Buprenorphine was not as effective in antagonizing the analgesic effects of higher efficacy agonists.

What about self-administration? Does the same phenomenon hold true for that effect?

Methods

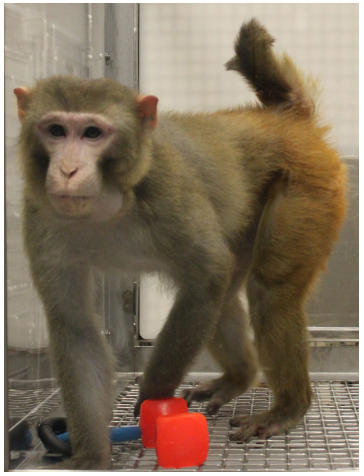
Winger & Woods Drug & Alcohol Dependence (2001)

Species: Rhesus monkeys

Assay: IV drug self-administration

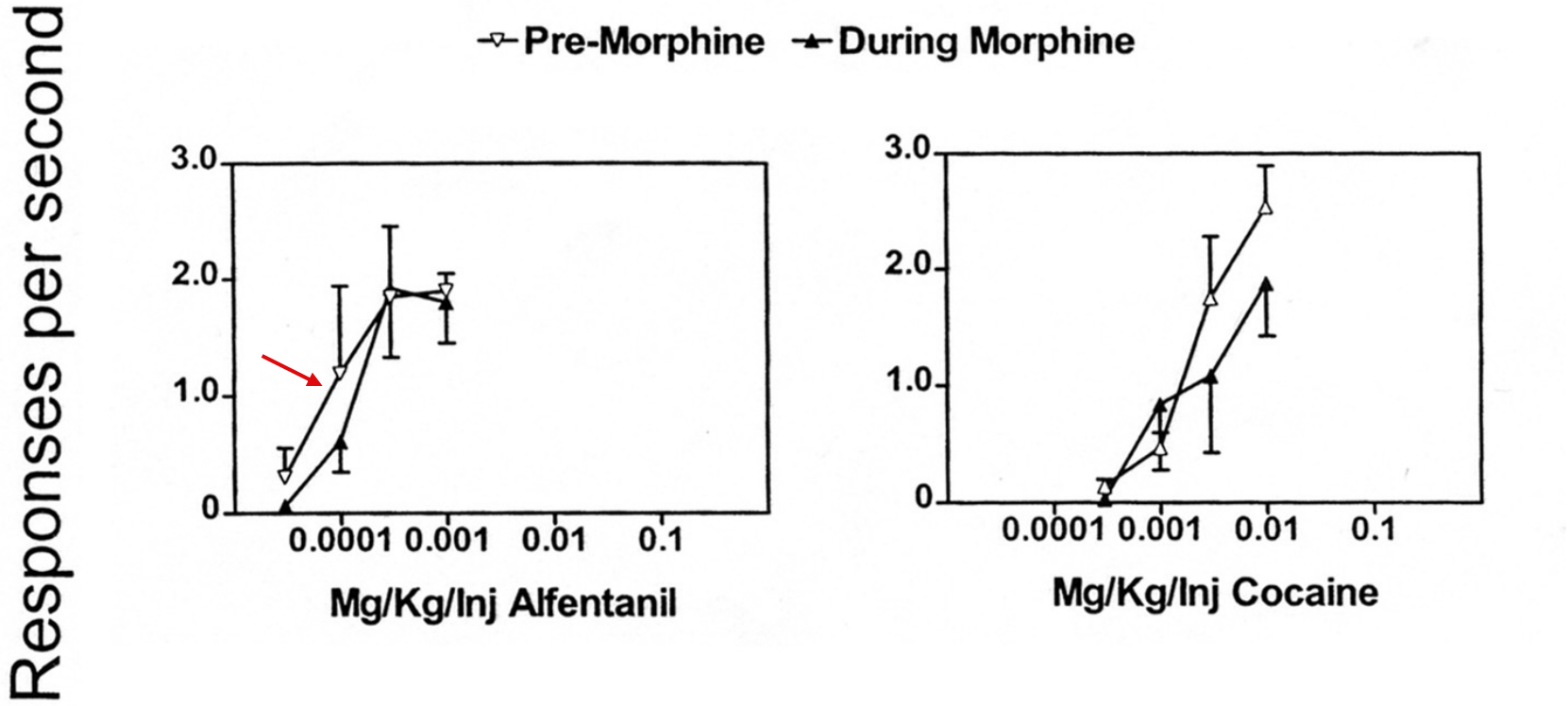
Dependent measure: Rate of responding

(responses/sec)

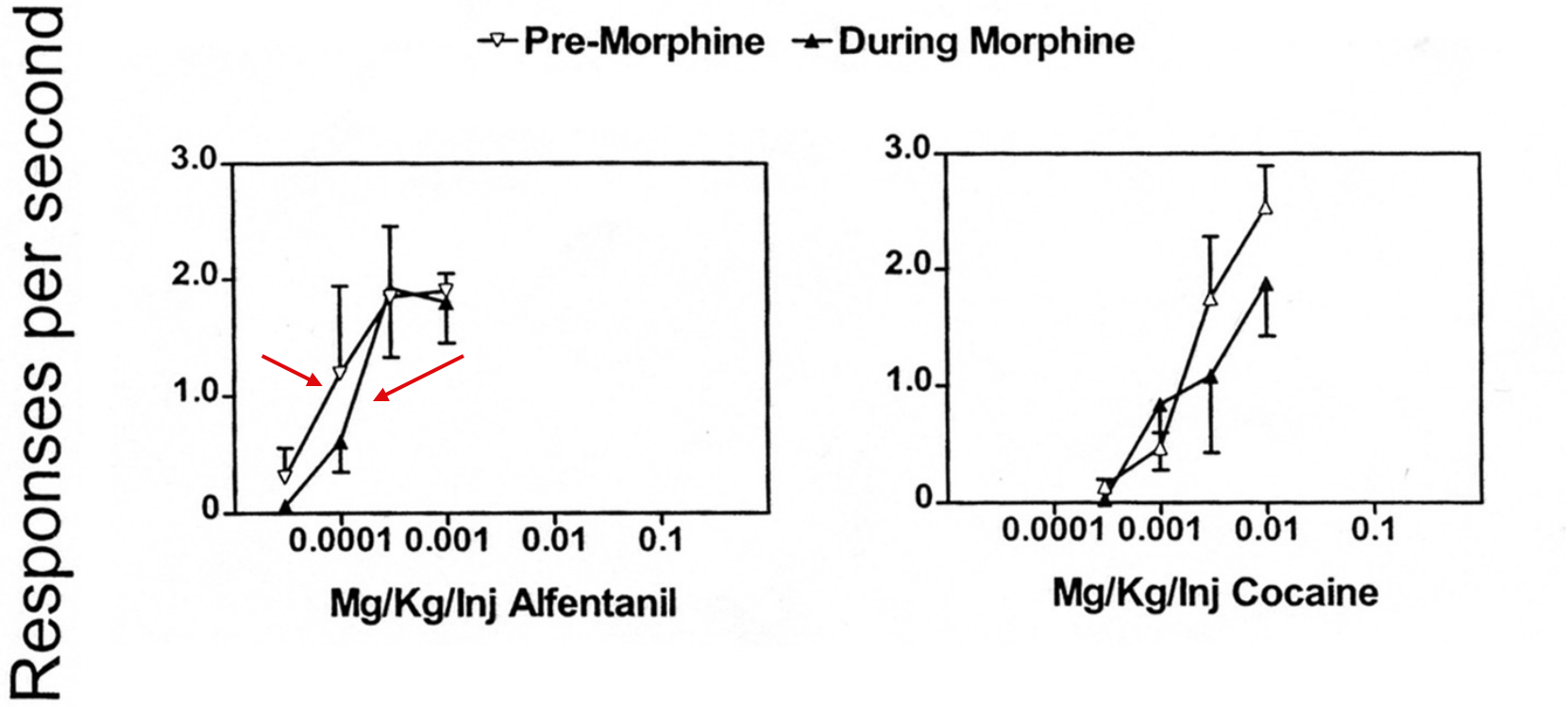


Maintenance drug: Morphine

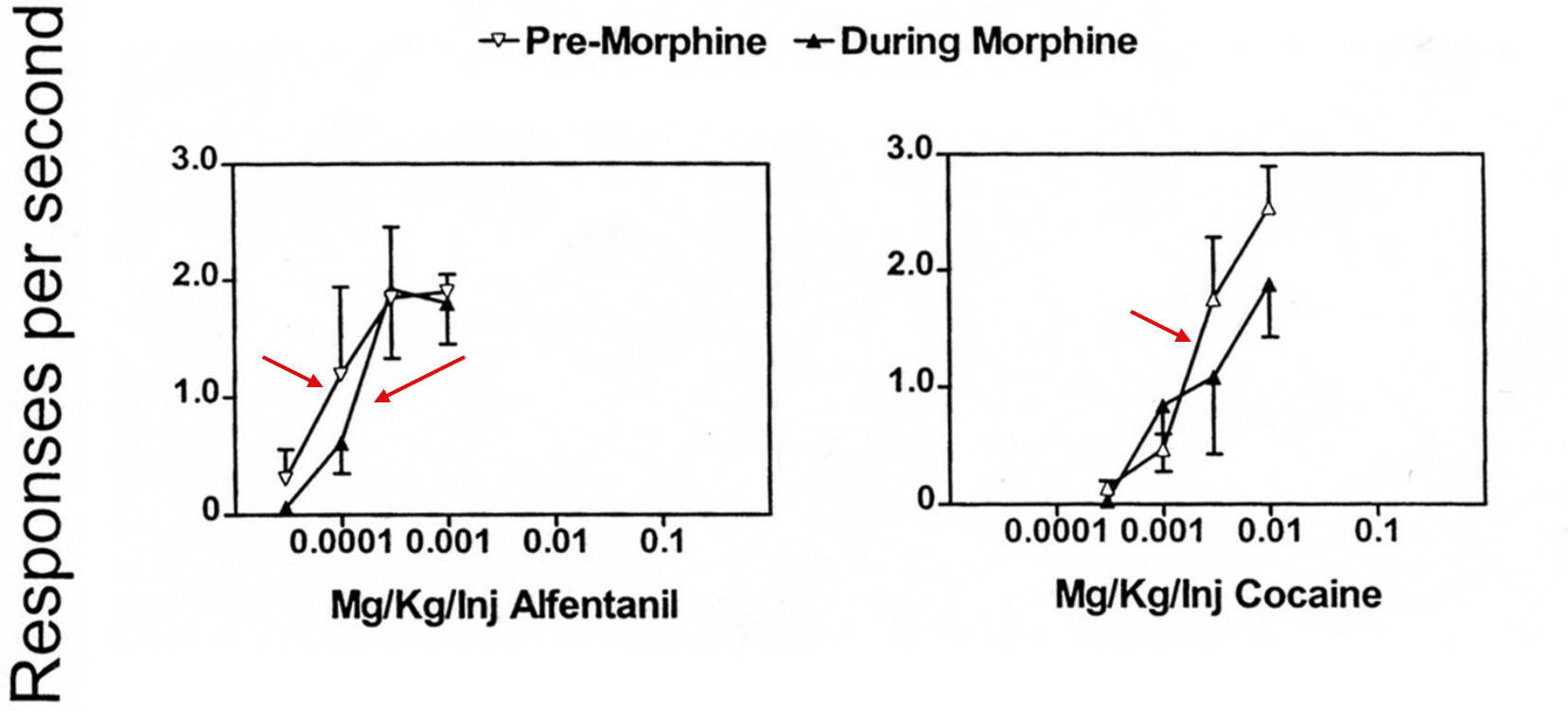
Test drugs: Alfentanil, heroin, morphine, nalbuphine, buprenorphine, and cocaine



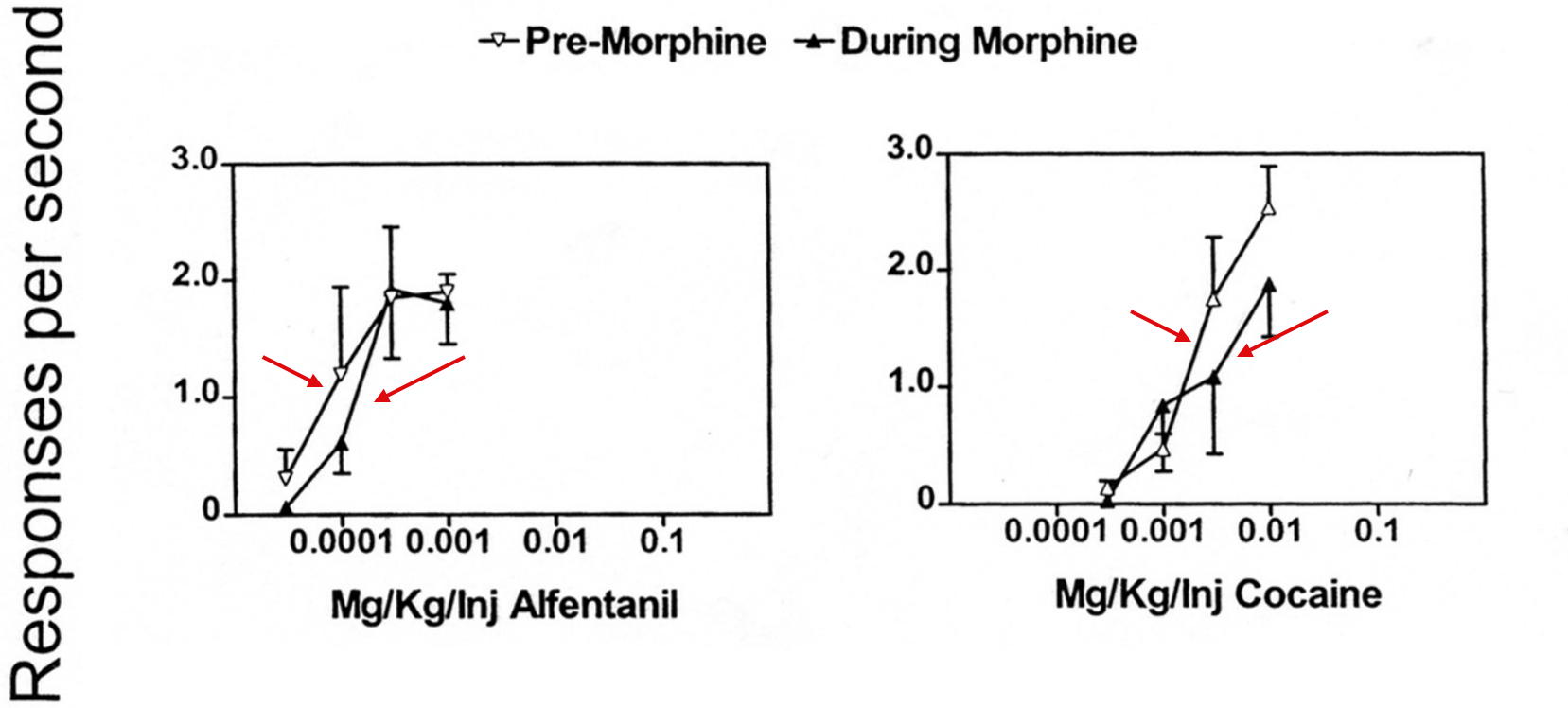
Winger & Woods Drug & Alcohol Dependence (2001) 62: 181-189



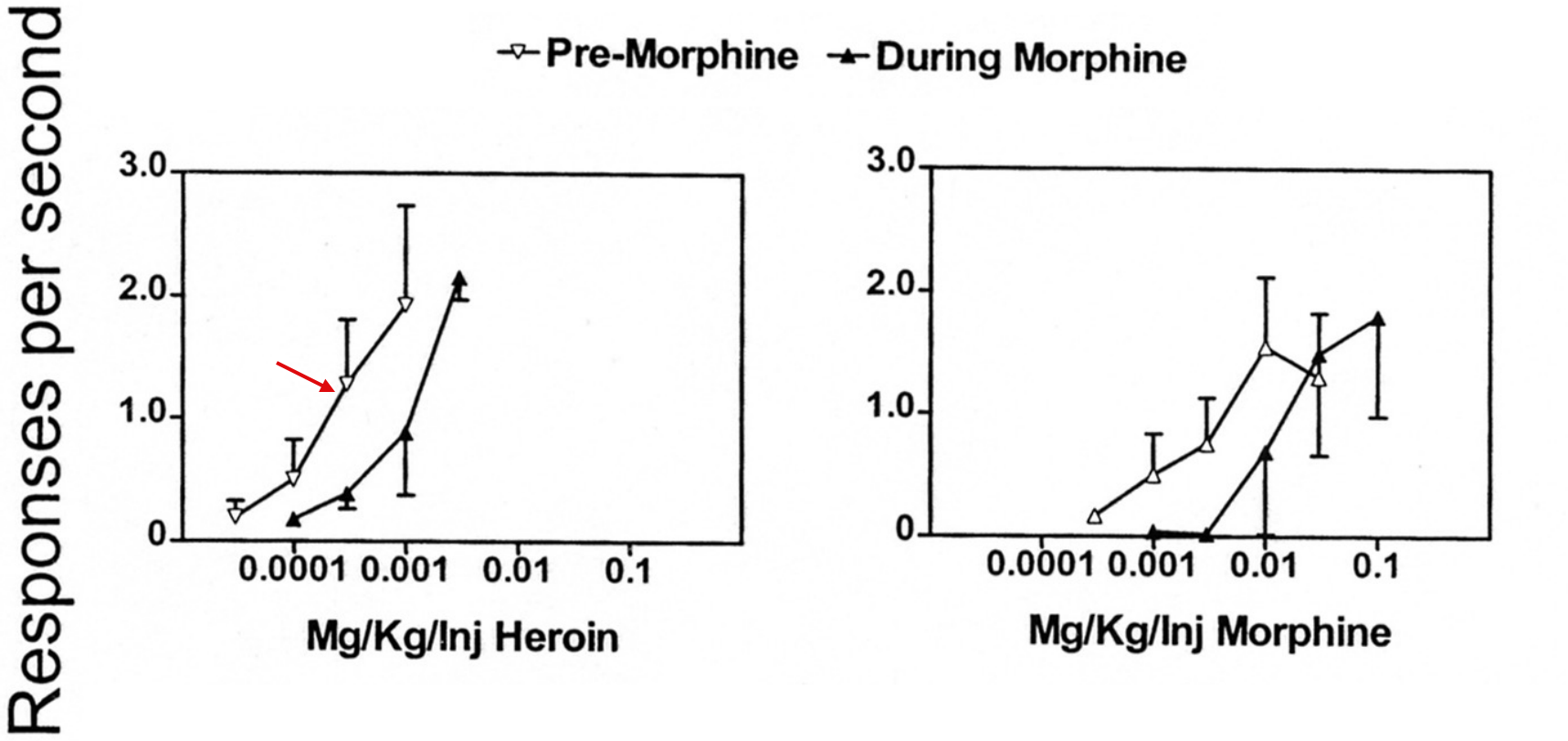
Winger & Woods Drug & Alcohol Dependence (2001) 62: 181-189



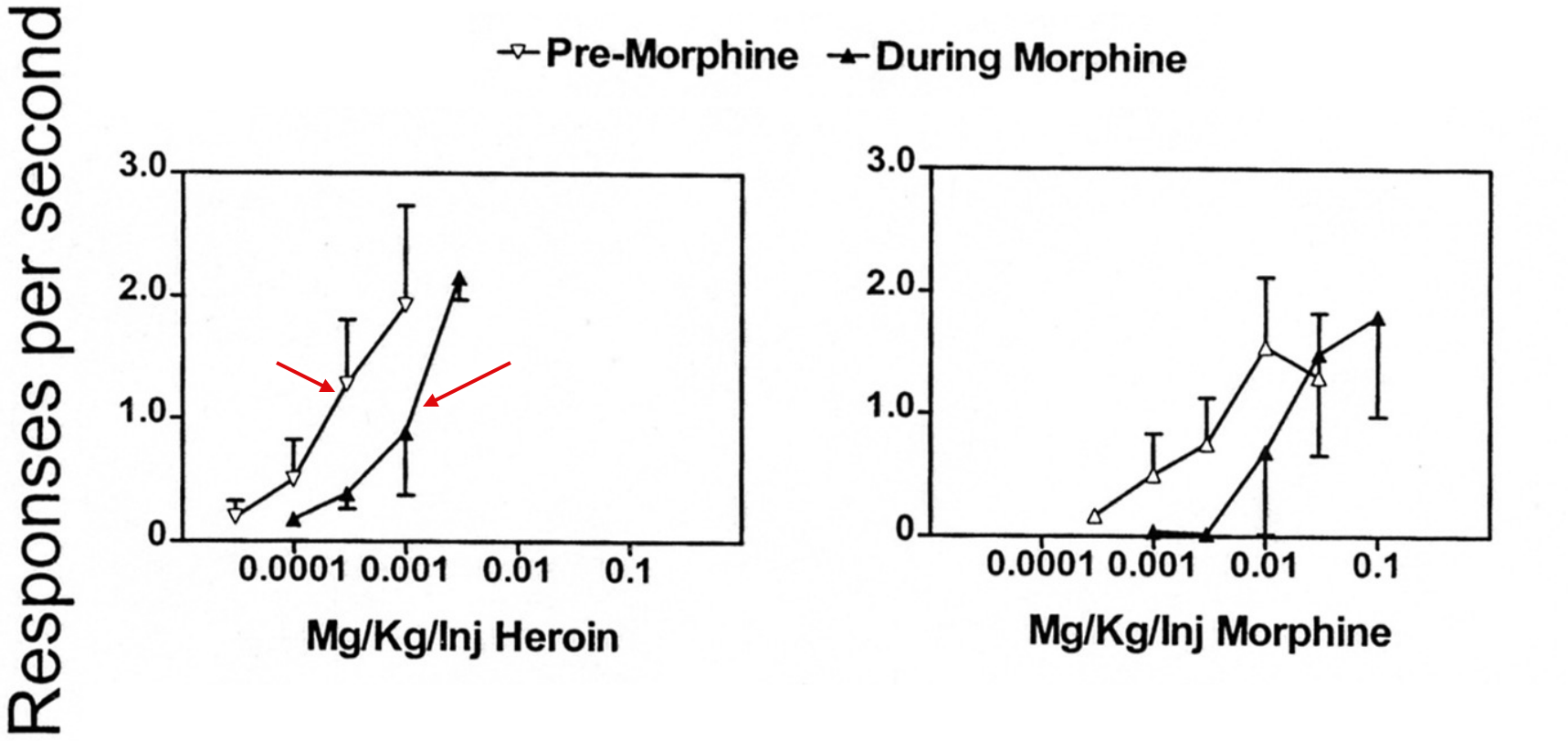
Winger & Woods Drug & Alcohol Dependence (2001) 62: 181-189



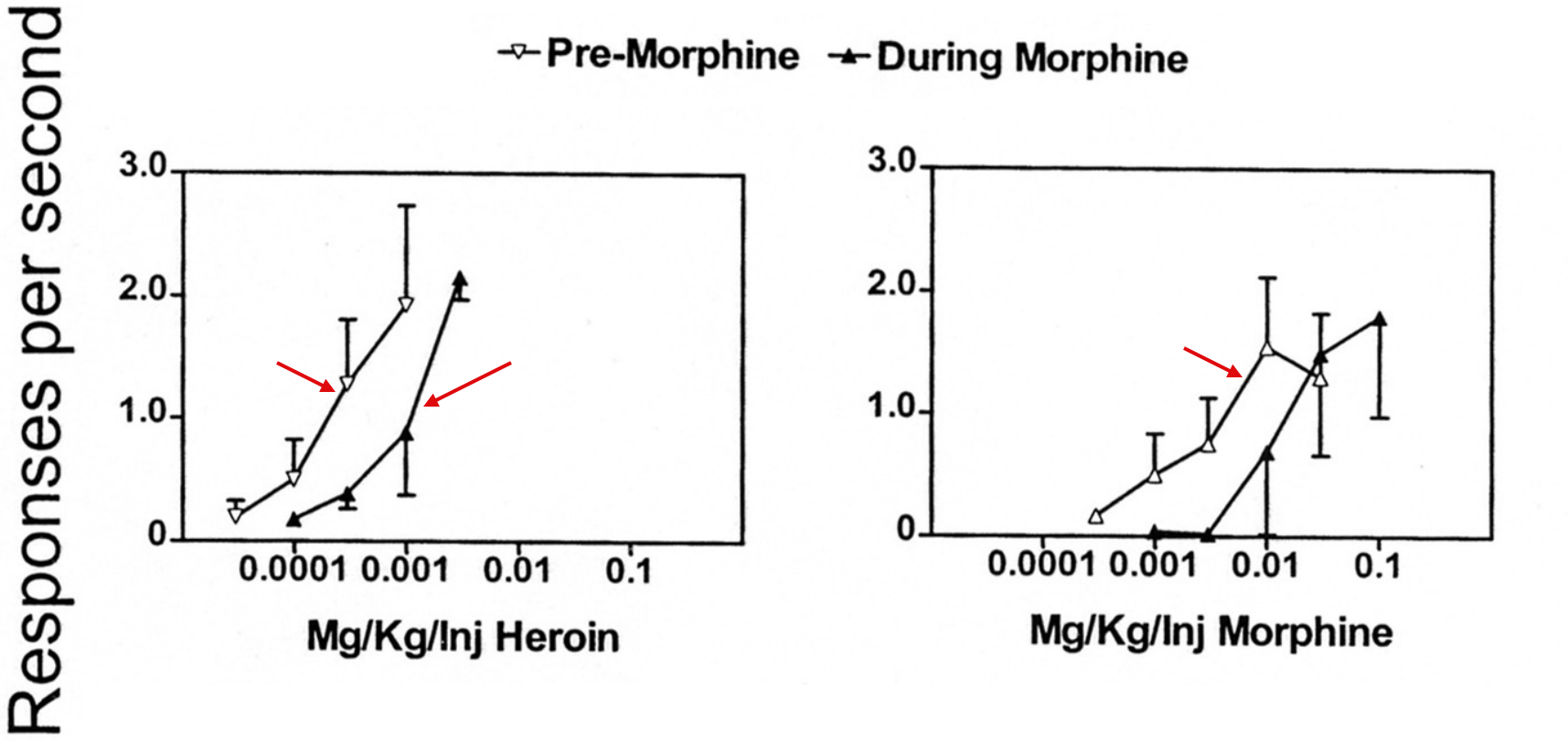
Winger & Woods Drug & Alcohol Dependence (2001) 62: 181-189



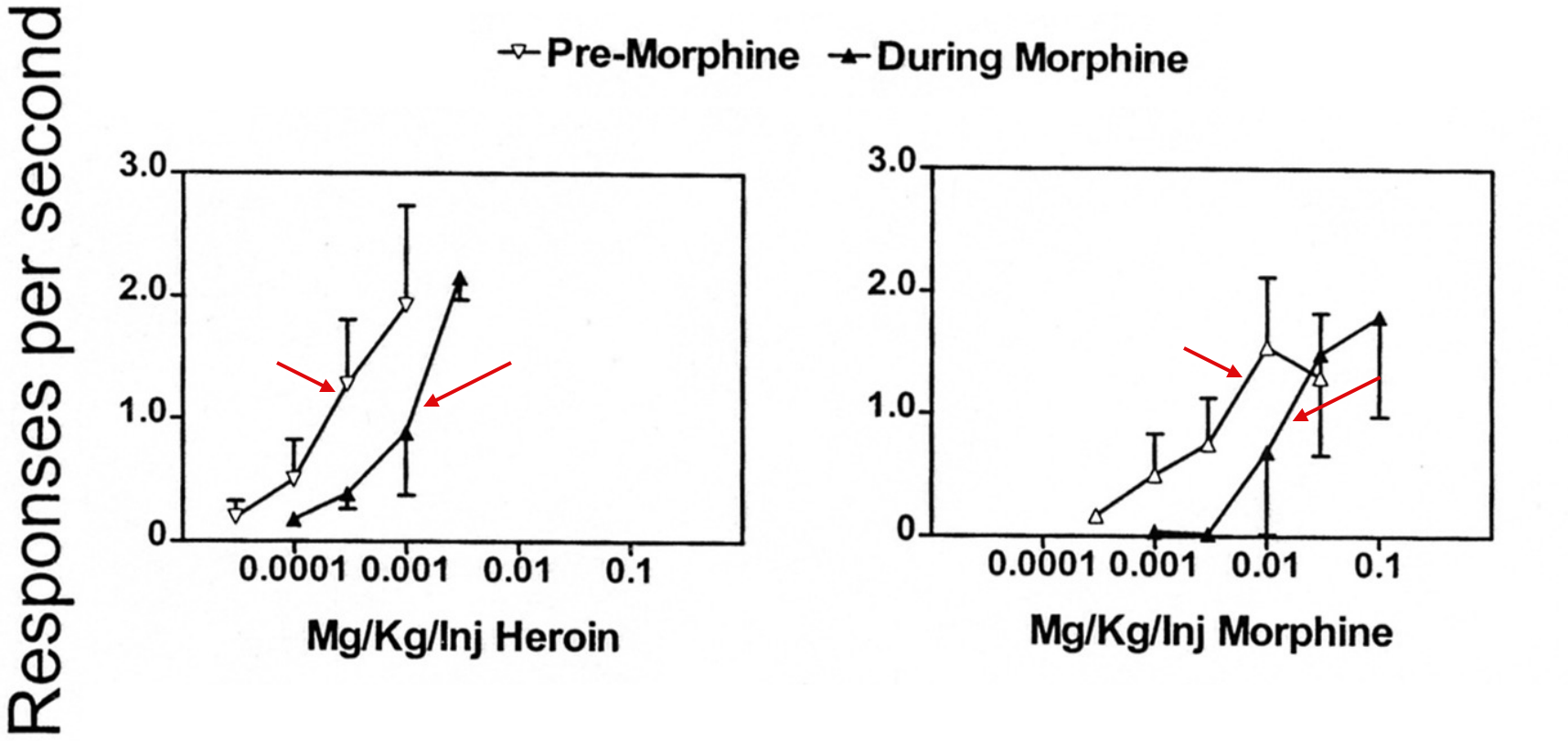
Winger & Woods Drug & Alcohol Dependence (2001) 62: 181-189



Winger & Woods Drug & Alcohol Dependence (2001) 62: 181-189



Winger & Woods Drug & Alcohol Dependence (2001) 62: 181-189



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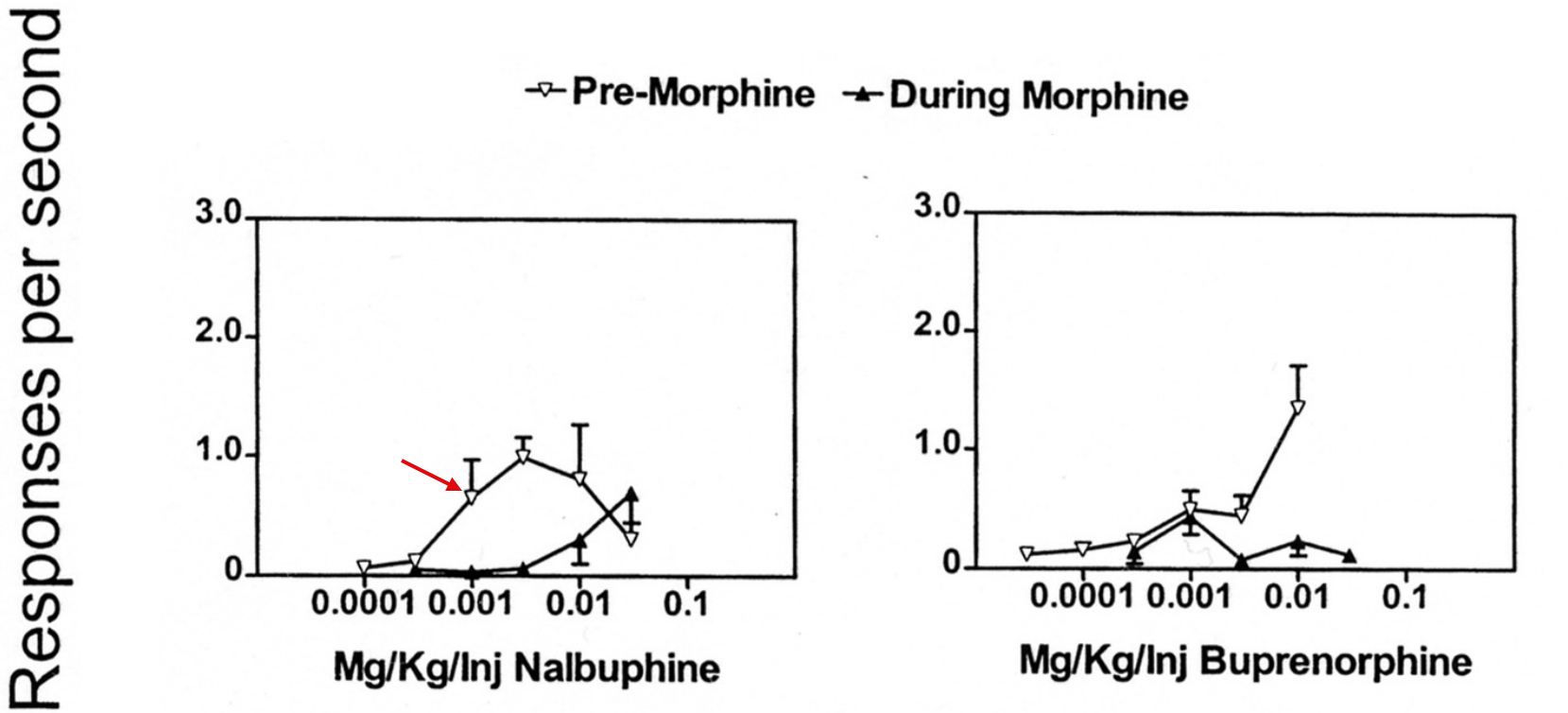
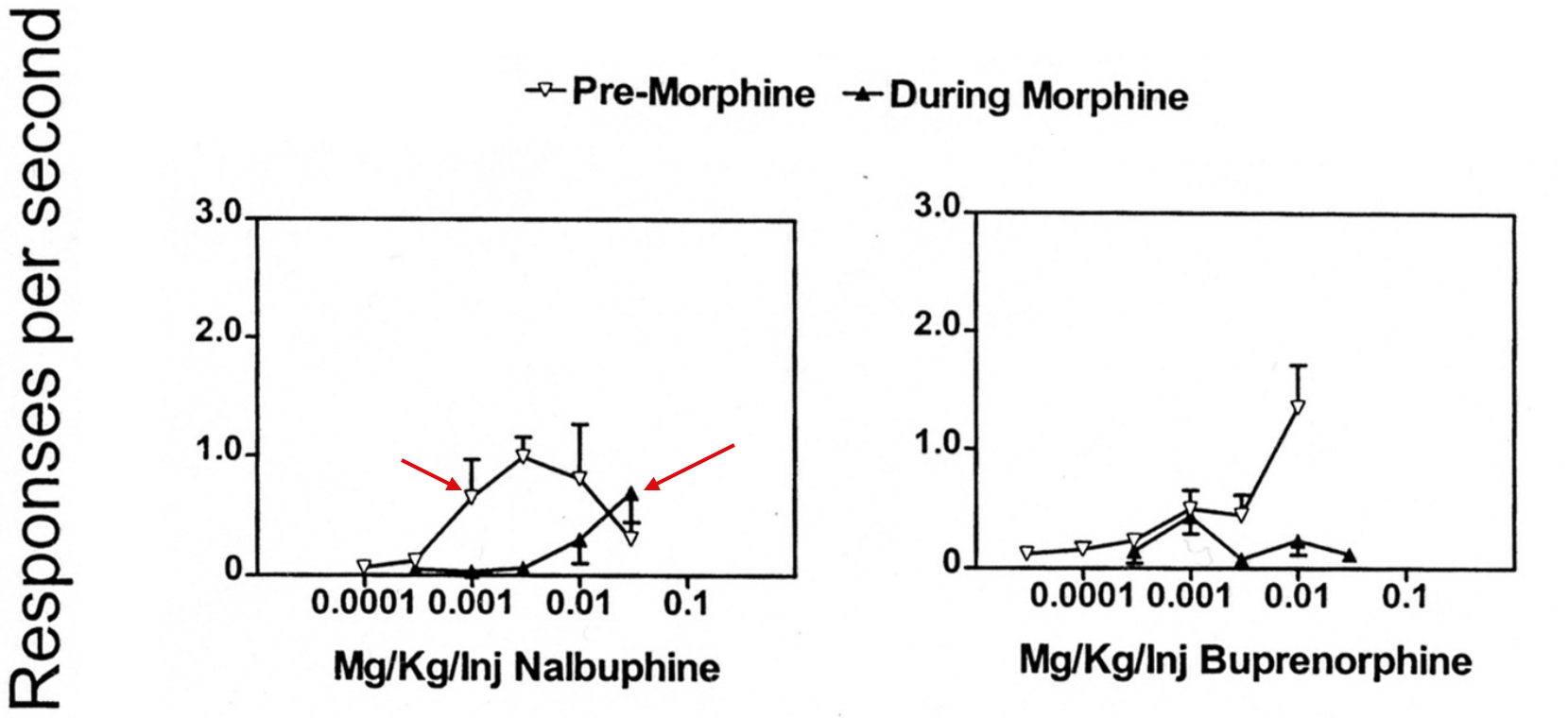
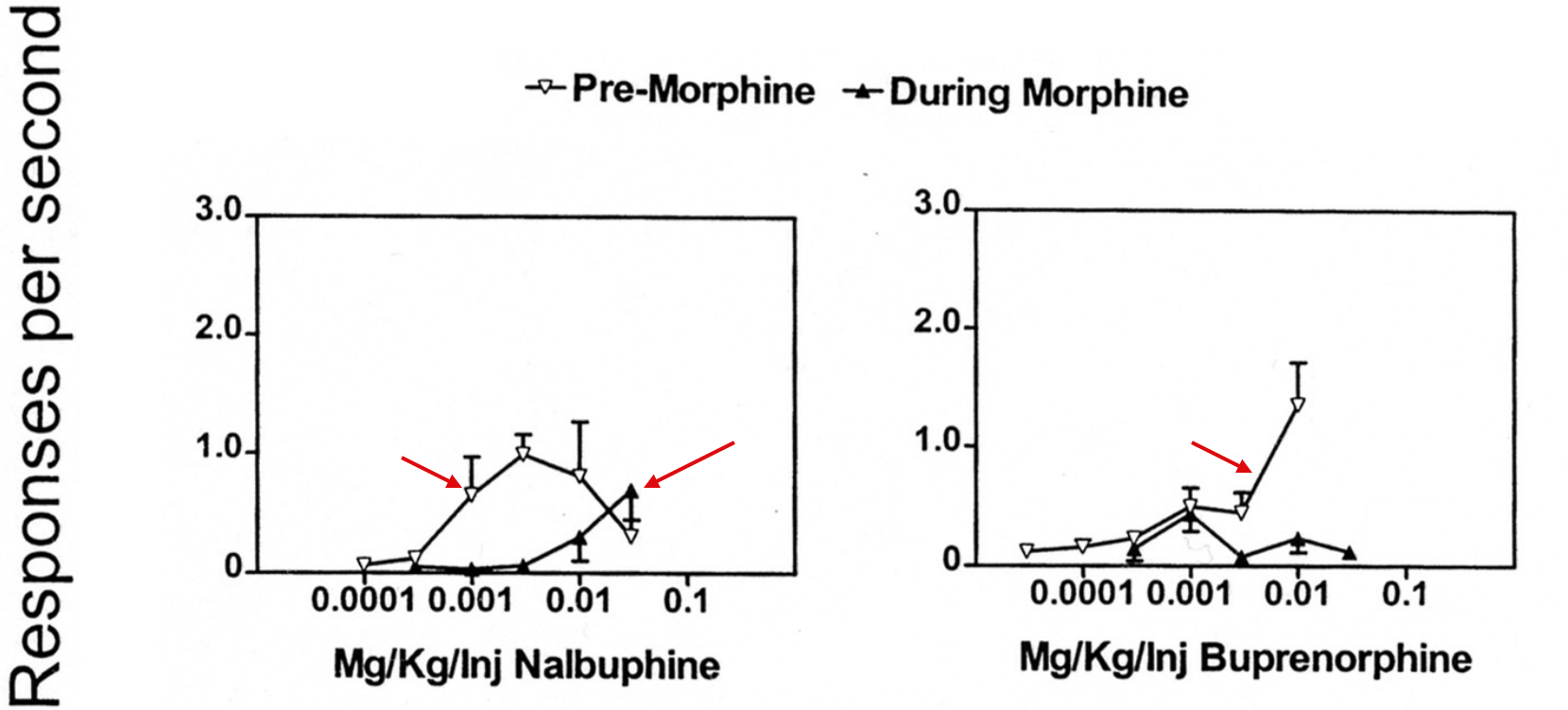


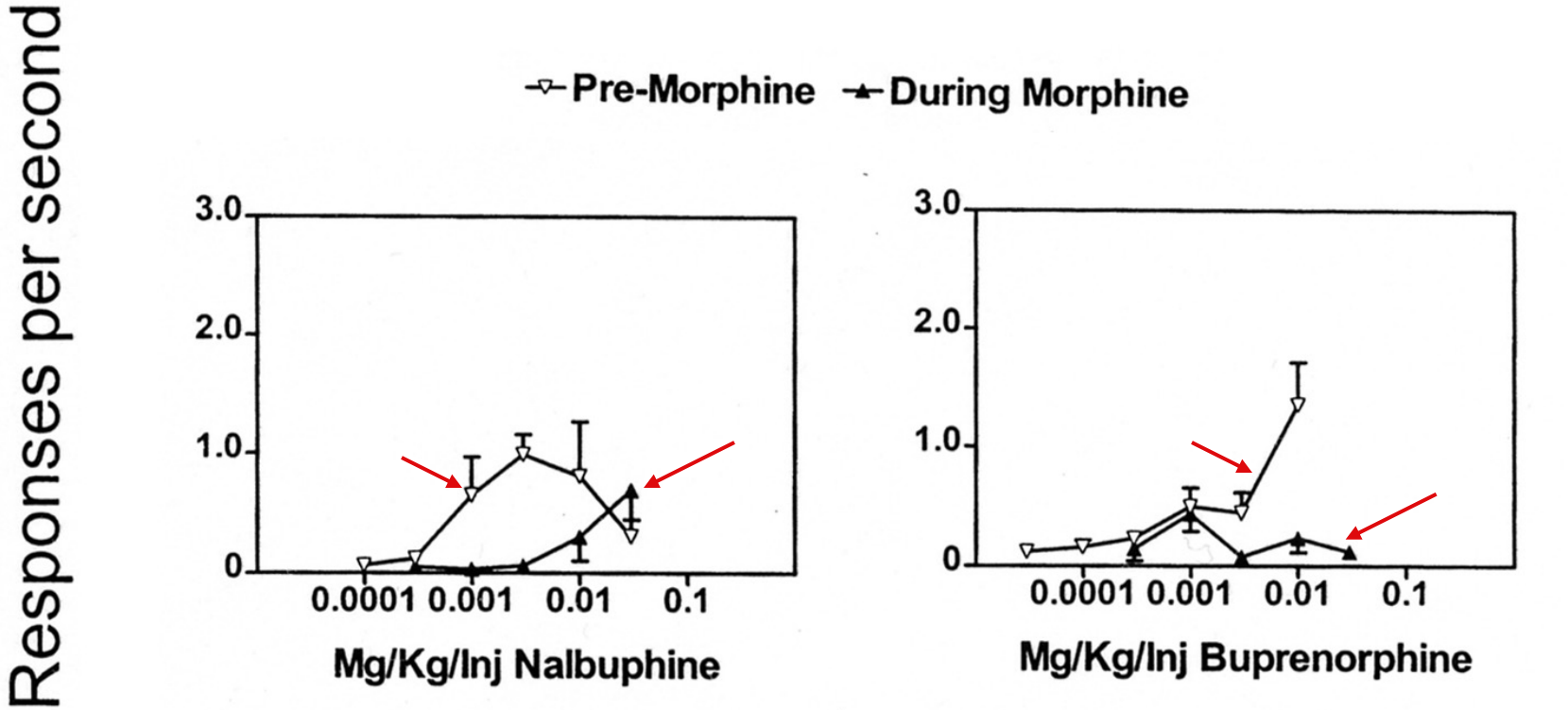
Winger & Woods Drug & Alcohol Dependence (2001) 62: 181-189



Winger & Woods Drug & Alcohol Dependence (2001) 62: 181-189



Winger & Woods Drug & Alcohol Dependence (2001) 62: 181-189



Winger & Woods Drug & Alcohol Dependence (2001) 62: 181-189

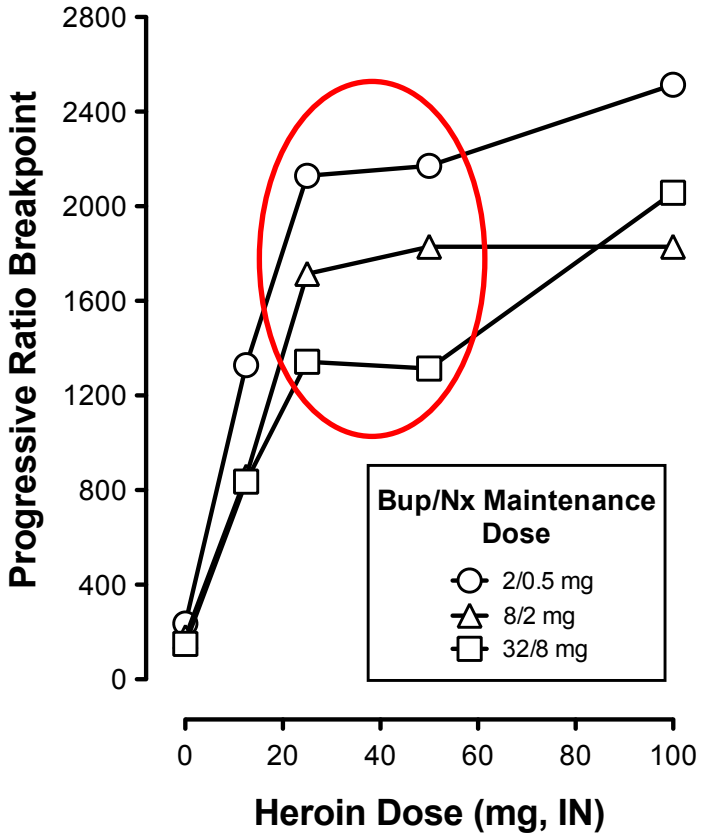
Assay	Species	Authors
Drug Discrimination	Rats	Young, Kapitsopoulos, & Makhay, 1991
Analgesia	Rats	Paronis & Holtzman, 1992
Drug Discrimination	Rats	Paronis & Holtzman, 1994
Analgesia	Mice	Duttaroy & Yoburn, 1995
Analgesia	Monkeys	Walker, Zernig, & Woods, 1995
Analgesia	Rats	Walker, Zernig, & Young, 1998
Analgesia	Monkeys	Pitts, Allen, Walker, & Dykstra, 1998
Response rates for food	Rats	Smith & Picker, 1998
Analgesia	Rats	Walker & Young, 2001
Analgesia	Rats	Barrett, Cook, Terner, Craft, & Picker, 2001
Self-administration	Monkeys	Winger & Woods, 2001
Drug Discrimination	Rats	Walker & Young, 2002
Drug Discrimination	Pigeons	Barrett, Smith, & Picker, 2003
Analgesia & Resp for food	Monkeys	Negus, Brandt, Gatch, & Mello, 2003

How translatable are these findings to humans?

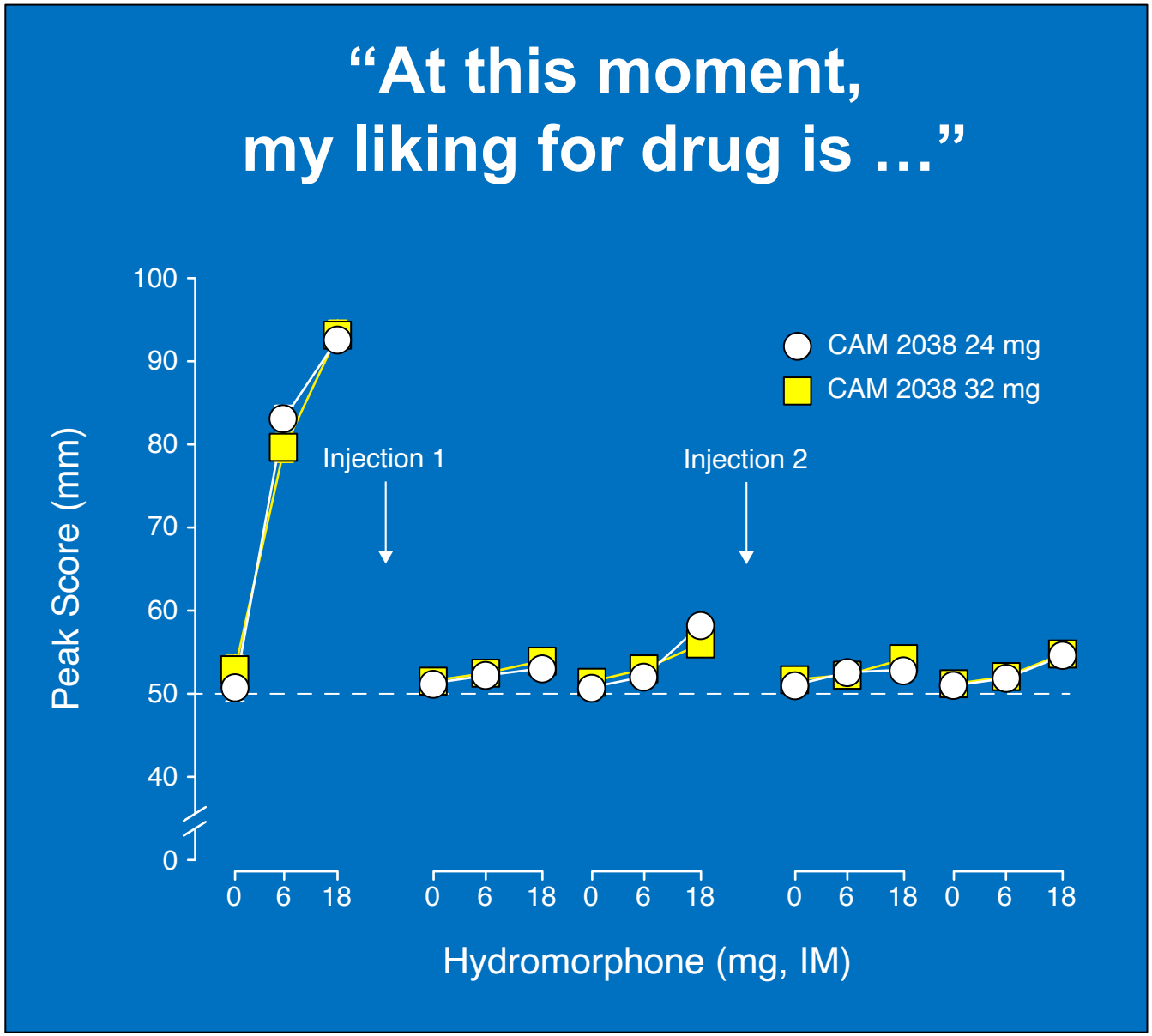
Buprenorphine/Naloxone Maintenance and Intranasal Heroin Self-administration

Comer, Walker, & Collins Psychopharmacol (2005) 181: 664-675

Bup/Nx produced a dose-related reduction in heroin self-administration, but the effects of heroin were still robust



Comer, Walker, & Collins Psychopharmacol (2005) 181: 664-675



A weeklong formulation of injectible buprenorphine reduced hydromorphone-induced drug liking in humans.

Walsh, Comer, et al (2017) JAMA Psychiatry

What about fentanyl?

- No laboratory-based studies have measured the ability of buprenorphine (or methadone or naltrexone) to antagonize the effects of fentanyl in humans
- One retrospective cohort study showed that treatment retention and opioid abstinence at 6 months after initiation of buprenorphine did not differ in patients who tested positive for fentanyl versus heroin at initiation of buprenorphine treatment (Wakeman et al., 2019) – but small sample sizes
- Another retrospective cohort study showed that treatment retention at 12 months after initiation of methadone did not differ in patients who tested positive versus negative for fentanyl at initiation of treatment (Stone et al., 2020) – but fentanyl use during treatment was common; no fatal overdoses

Initiation of Buprenorphine Treatment

Withdrawal can be severe in fentanyl users who are transitioning to buprenorphine

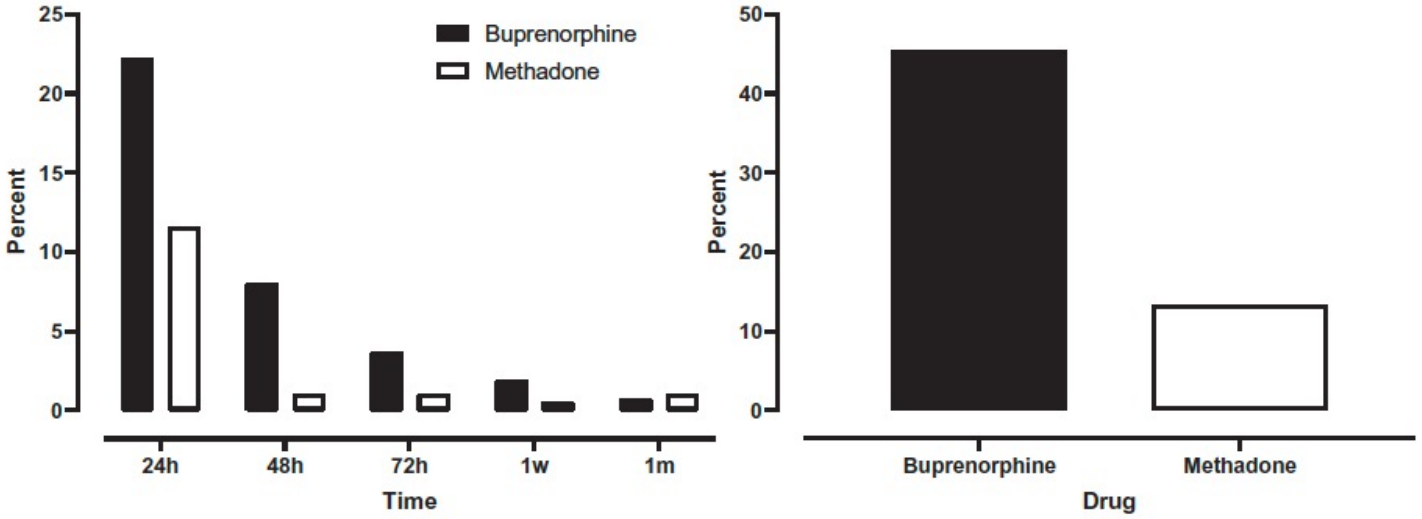


FIGURE 1. (LEFT) Percentage of patients who endorsed "probably" or "definitely" using fentanyl and who reported severe withdrawal after use of buprenorphine (n = 250) or methadone (n = 30) as a function of the shortest amount of time endorsed (24, 48, or 72 hours, 1 week, and 1 month) after fentanyl use. (RIGHT) Percentage of patients who endorsed "probably" or "definitely" using fentanyl and who reported severe withdrawal after use of buprenorphine (n = 69) or methadone (n = 20) after taking fentanyl; only patients with experience with both buprenorphine and methadone after fentanyl use were included this analysis.

Varshneya et al. J Addict Med (2021)

Initiation of Buprenorphine Treatment

The American Journal on Addictions, 30: 83–87, 2021

ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1111/ajad.13069

Method for Successfully Inducting Individuals Who Use Illicit Fentanyl Onto Buprenorphine/Naloxone

Denis Antoine, MD, Andrew S. Huhn, PhD, MBA, Eric C. Strain, MD, Gavin Turner, BS, Jasmyne Jardot, BA, Alexis S. Hammond, MD, PhD, Kelly E. Dunn, PhD, MBA

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland

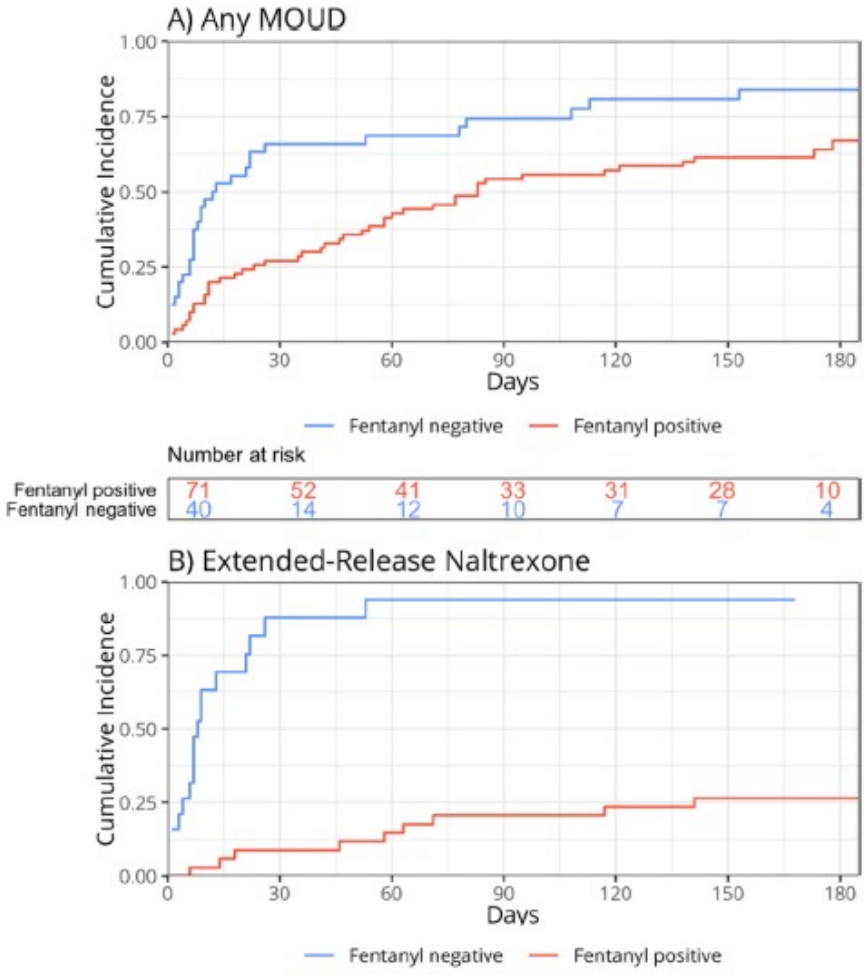
COMMENTARY

A Plea From People Who Use Drugs to Clinicians: New Ways to Initiate Buprenorphine are Urgently Needed in the Fentanyl Era

Kimberly L. Sue, MD, PhD, Shawn Cohen, MD, Jess Tilley, and Avi Yocheved

J Addict Med • Volume 00, Number 00, Month/Month 2022

Initiation of Naltrexone Treatment



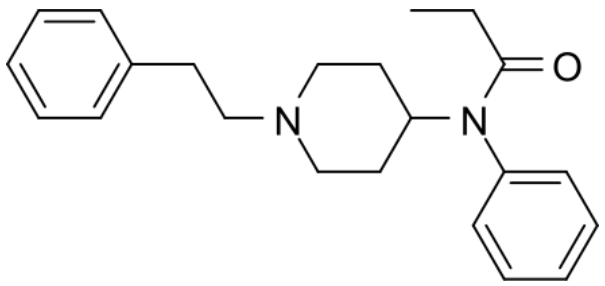
Fentanyl+ patients half as likely to initiate treatment overall

Fentanyl+ patients 11x less likely to initiate treatment with naltrexone

No evidence that fentanyl related to bup initiation

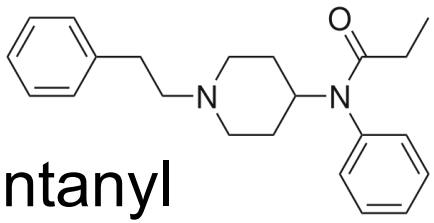
Cook et al. DAD (2021)

What can we conclude so far?

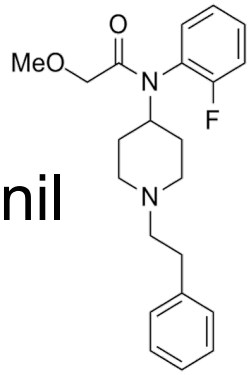


- ✓ Fentanyl is potent, has a rapid onset of action, and is short acting
- ✓ Naltrexone is effective in preventing the fentanyl-induced responses but is less effective against carfentanil (preclinical data)
- ✓ Naloxone appears to be less effective against fentanyl overdose (preclinical data and clinical case reports)

Unanswered Clinical Questions

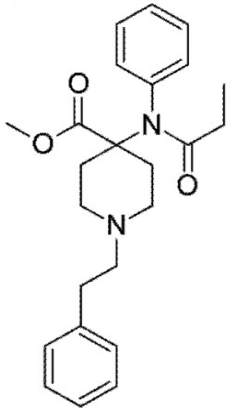


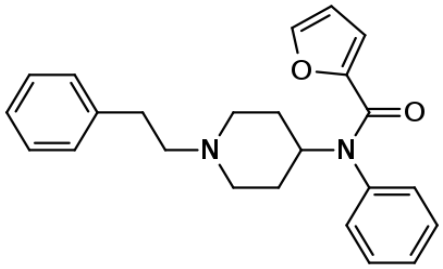
Fentanyl



Ocfentanil

Carfentanil





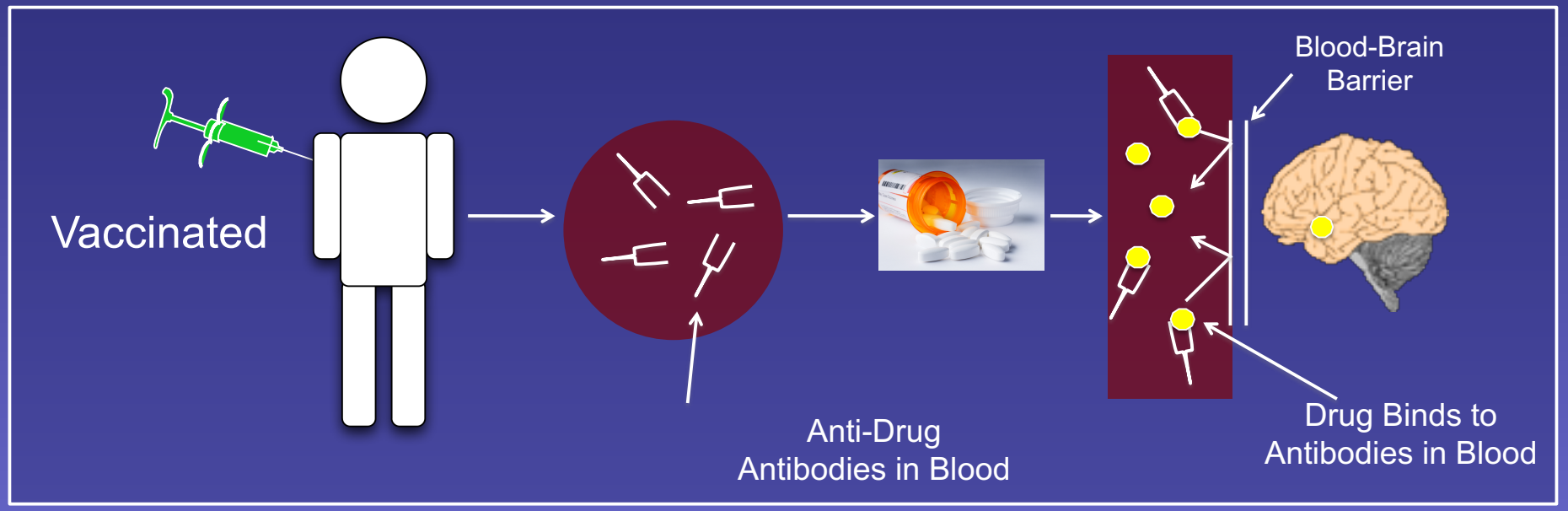
Furanyl Fentanyl

- ✓ How well do methadone, buprenorphine, and naltrexone work for treating OUD in patients using fentanyl? Retrospective studies suggest that buprenorphine and methadone are effective.
- ✓ But what about the analogs?
- ✓ How do we most effectively transition patients from fentanyl to these treatment medications?
- ✓ How do we most effectively manage fentanyl-related overdoses?

So what do we do?

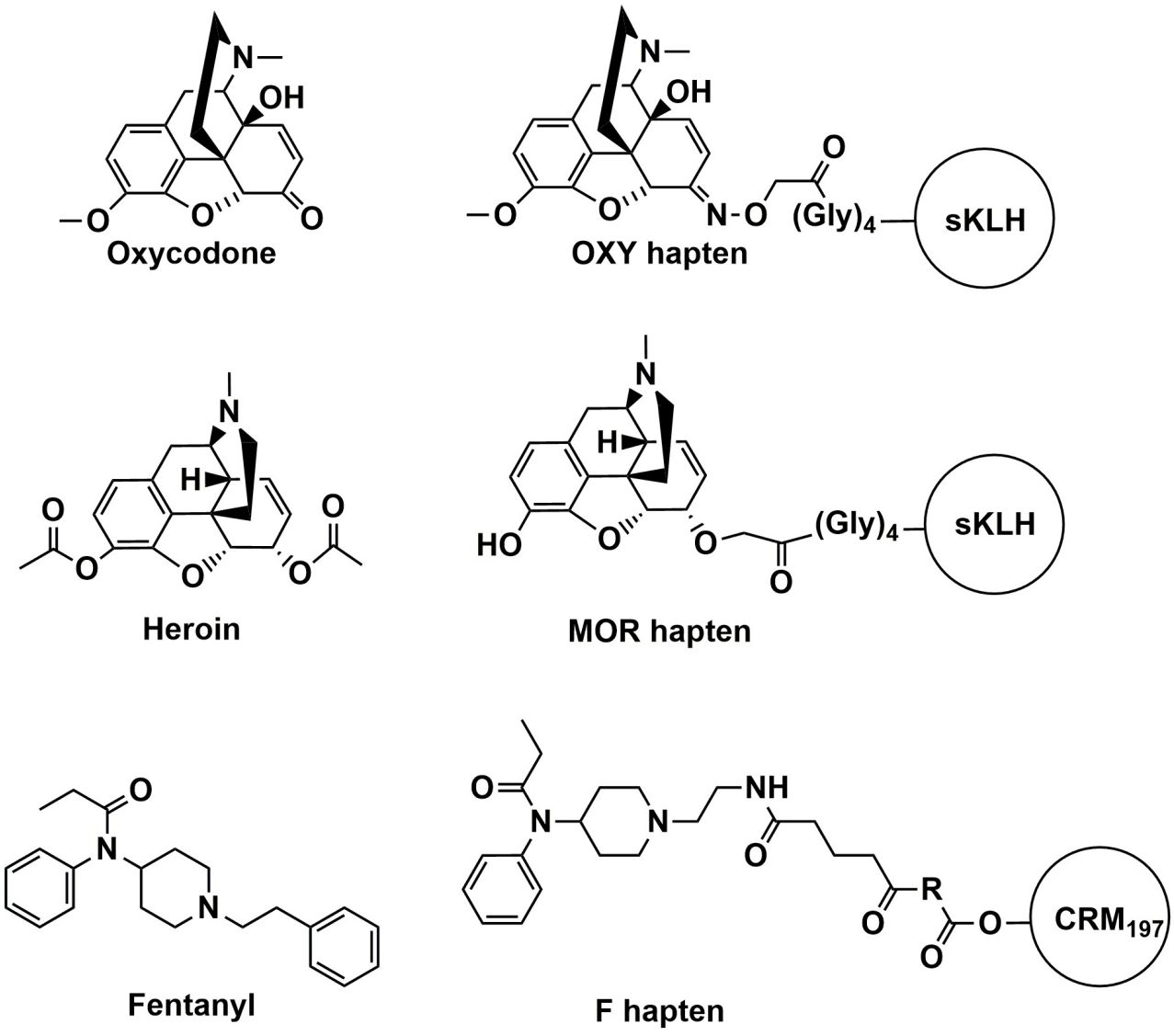
Continue to develop medications

Vaccines for illicit drug use generate antibodies that bind drug in plasma and block entry to the brain



A series of injections are given over several months in order to achieve maximal antibody production

Candidate vaccines for heroin and prescription opioids

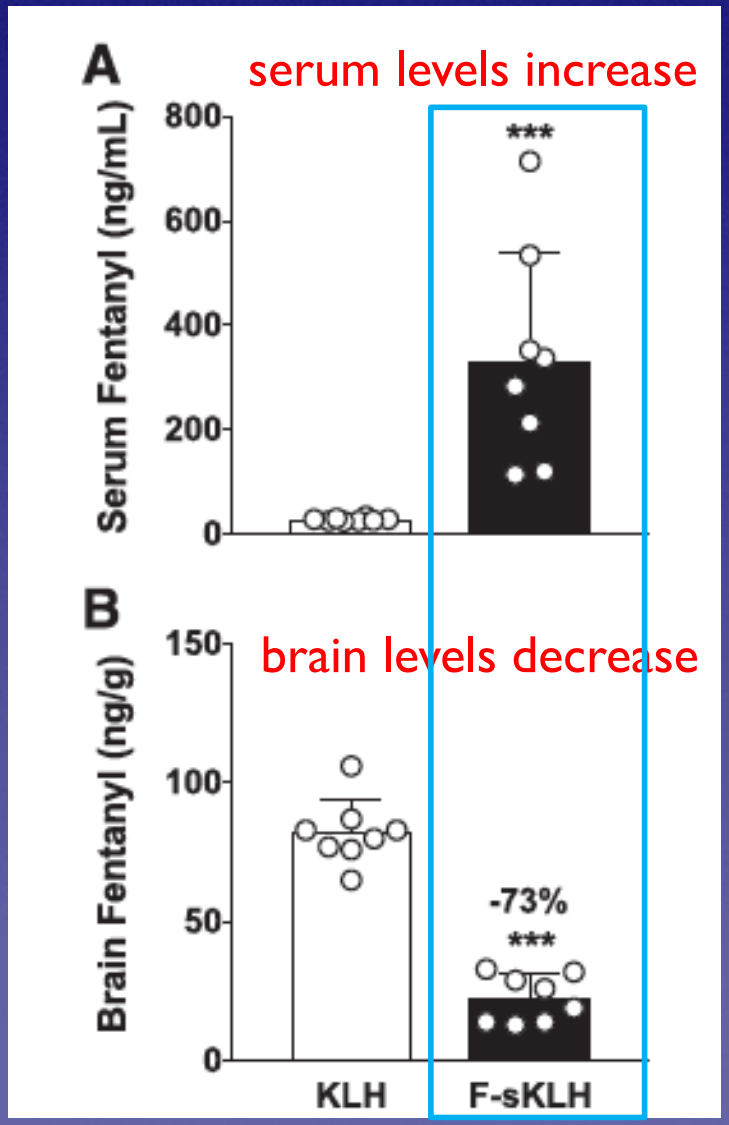


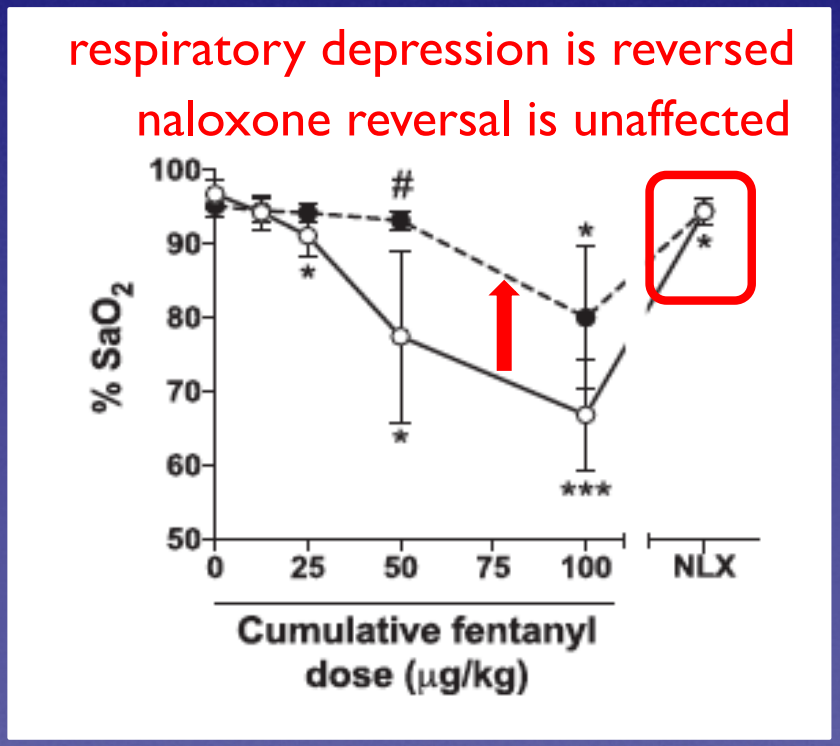
OXY-KLH targets oxycodone, hydrocodone, oxymorphone

M-KLH targets heroin, 6-AM, and morphine

F-CRM targets fentanyl and its analogs

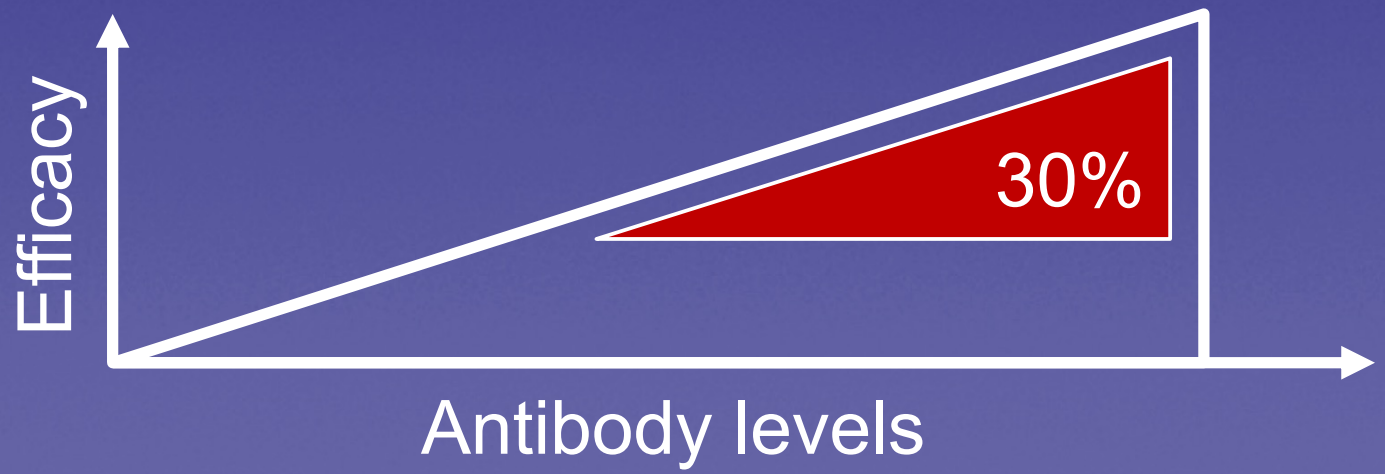
Fentanyl Vaccine: Preclinical Data





Challenge. Identify immunological mechanisms and biomarkers of vaccine efficacy to accelerate translation

First-generation nicotine and cocaine vaccines showed clinical proof of efficacy in ~30% of immunized subjects that achieved highest antibody levels

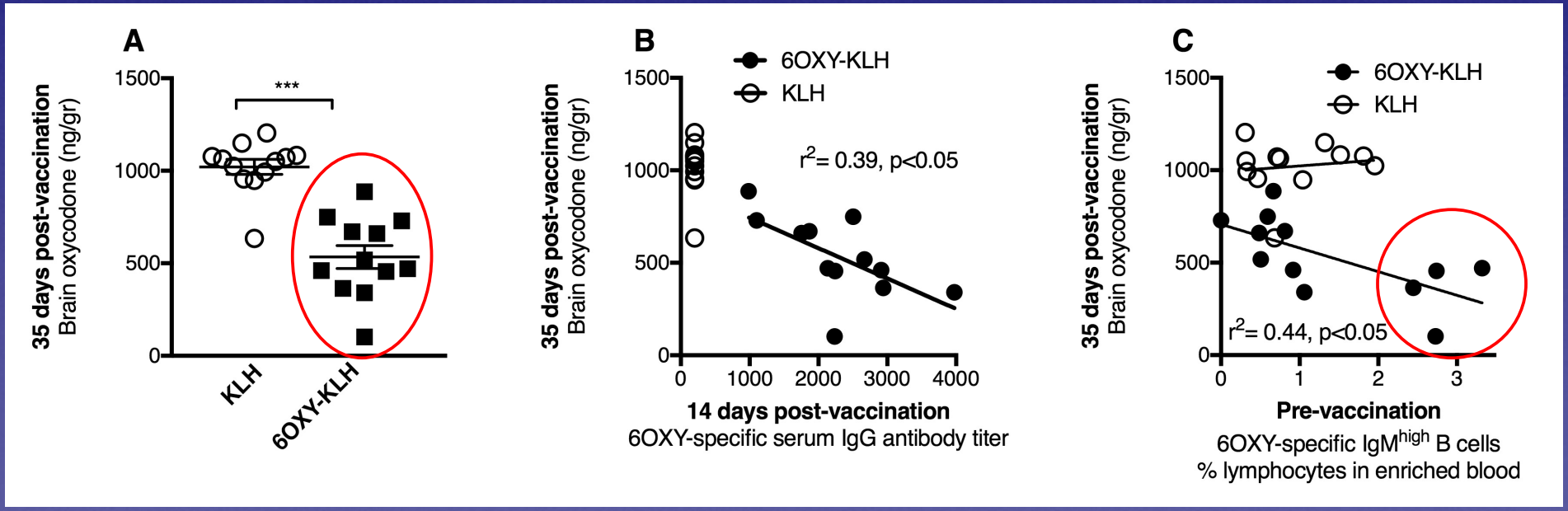


Biomarker. Vaccine efficacy is predicted by early antibodies and pre-immunization B cell frequency in mice

A. OXY-KLH efficacy in blocking oxycodone to brain

B. Antibody titers vs. efficacy IgG subclasses vs. efficacy

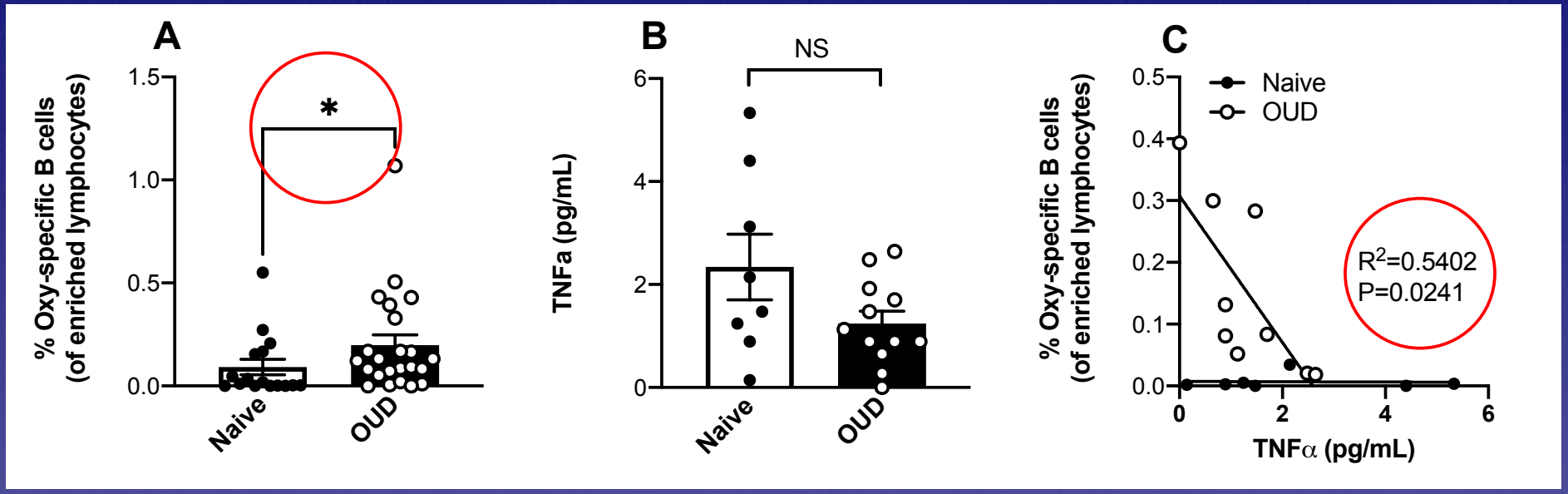
C. OXY-specific B cell frequency vs. efficacy



Laudenbach et al., J. Immunology 2015
Laudenbach et al., Vaccine 2015
Taylor et al., J. Immunol. Methods 2014

Phase I trial includes exploratory biomarkers to select or stratify patients

Comparison of opioid users and naïve individuals' opioid-specific B cells and TNFα expression



- Significant difference in the frequency of opioid-specific B cells
- No difference in the expression of TNFα
- Correlation between TNFα expression and opioid-specific B cells only for opioid users

Is TNFα a viable biomarker to predict vaccine clinical efficacy?

THANK YOU!

Jermaine Jones, PhD
Rachel Luba, PhD
Jeanne Manubay, MD
Shanthi Mogali, MD
Felipe Castillo, MD
Claudia Tindall, NP
Janet Murray, RN
Nicholas Allwood, BS
Rebecca Abbott, BS
Freymon Perez, BS

UG3DA047711 (Comer)
T32DA007294 (Levin)

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