Oral and intravenous oxymorphone: Relative potency compared to other μ opioid agonists in humans

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Disclosures

Shanna Babalonis has no conflicts of interest related to the presented work

Background

Oxymorphone is a semisynthetic opioid agonist, exhibits high degree of μ-opioid receptor selectivity and intrinsic activity

Oral, parenteral formulations of oxymorphone were approved by the FDA in 1959 (Numorphan®)

In 1979, the manufacturer voluntarily removed the oral products, citing commercial reasons[1]; however, there were reports of high rates of misuse[2]

Oral oxymorphone returned to the market in 2006 (Opana®, Opana® ER)

Since this time, oxymorphone misuse has increased; the extended-release product was removed from the market due to risks associated with misuse[1]

Little controlled data are available on the abuse potential of oxymorphone

1. FDA (2017). Drug Safety & Risk Management Advisory Committee and the Anesthetic & Analgesic Drug Products Advisory Committee (AADPAC), Briefing Documents.
2. Watkins TD, Chambers CD (1972) Oxymorphone Abuse Among Current Narcotic Addicts pp. 307-312.

Relative Potency of Oxymorphone

Two within-subject, double-blind, placebo-controlled studies were conducted to examine:

1) Relative abuse potential and relative potency of *oral* oxymorphone

2) Relative abuse potential and relative potency of *intravenous* oxymorphone

Relative Potency of Oxymorphone

Two placebo-controlled studies conducted to examine:

1) Relative abuse potential and relative potency of *oral* oxymorphone

2) Relative abuse potential and relative potency of intravenous oxymorphone

Oral Oxymorphone

Published potency estimates are based on several clinical trials with pain patients[3]

Indicates that oral oxymorphone is more potent than all listed comparators: twice as potent as oral oxycodone, hydrocodone, methadone; three times as potent as oral morphine

Oxymorphone	10 mg
Oxycodone	20 mg
Hydrocodone	20 mg
Methadone	20 mg
Morphine	30 mg

3.. Endo Pharmaceuticals (2016). Prescribing Information and Package Insert, Opana (oxymorphone hydrochloride). Malvern, PA.

Background

One previous controlled human laboratory study examined the pharmacodynamic effects of oral oxymorphone [4,5]

- Designed to evaluate the abuse liability of oxymorphone ER relative to oxycodone ER
- Doses were selected based on equianalgesic estimates
  - 2:1, oxycodone: oxymorphone
- The authors concluded that oxymorphone had less abuse liability than oxycodone
- However, inspection of the data suggested that comparable dose ranges were not evaluated
  - *Ex: pupil diameter measurements were not comparable across the matched dose conditions*

4. Schoedel KA et al (2011) Positive and negative subjective effects of extended-release oxymorphone versus controlled-release oxycodone in recreational opioid users. J Opioid Manag 7: 179-92.
5. Schoedel KA et al (2010) Reduced cognitive and psychomotor impairment with extended-release oxymorphone versus controlled-release oxycodone. Pain Physician 13: 561-73.

Oral Oxymorphone Study Aims

1) Examine the relative abuse liability and relative potency of oxymorphone compared to oxycodone employing a broad array of pharmacodynamic outcomes

2) Examine the analgesic response to both drugs using two experimental pain models

Participants and Methods

Participants were healthy adults who misused opioids

- 2 females, 7 males (8 Caucasian, 1 African American)
- mean age of 30.5 (±1.6) years
- reported 8 (± 0.8) days of prescription opioid misuse, past 30 days
- mean of 7 (± 1.7) years of opioid misuse

Randomized, within-subject crossover, and placebo-controlled design

Participants resided as inpatients for approximately 3 weeks and completed a total of 7 sessions

Each session was separated by at least 48 hours

Methods

Double-blind doses: oxymorphone (10, 20, 40 mg, PO)
oxycodone (10, 20, 40 mg, PO)
placebo

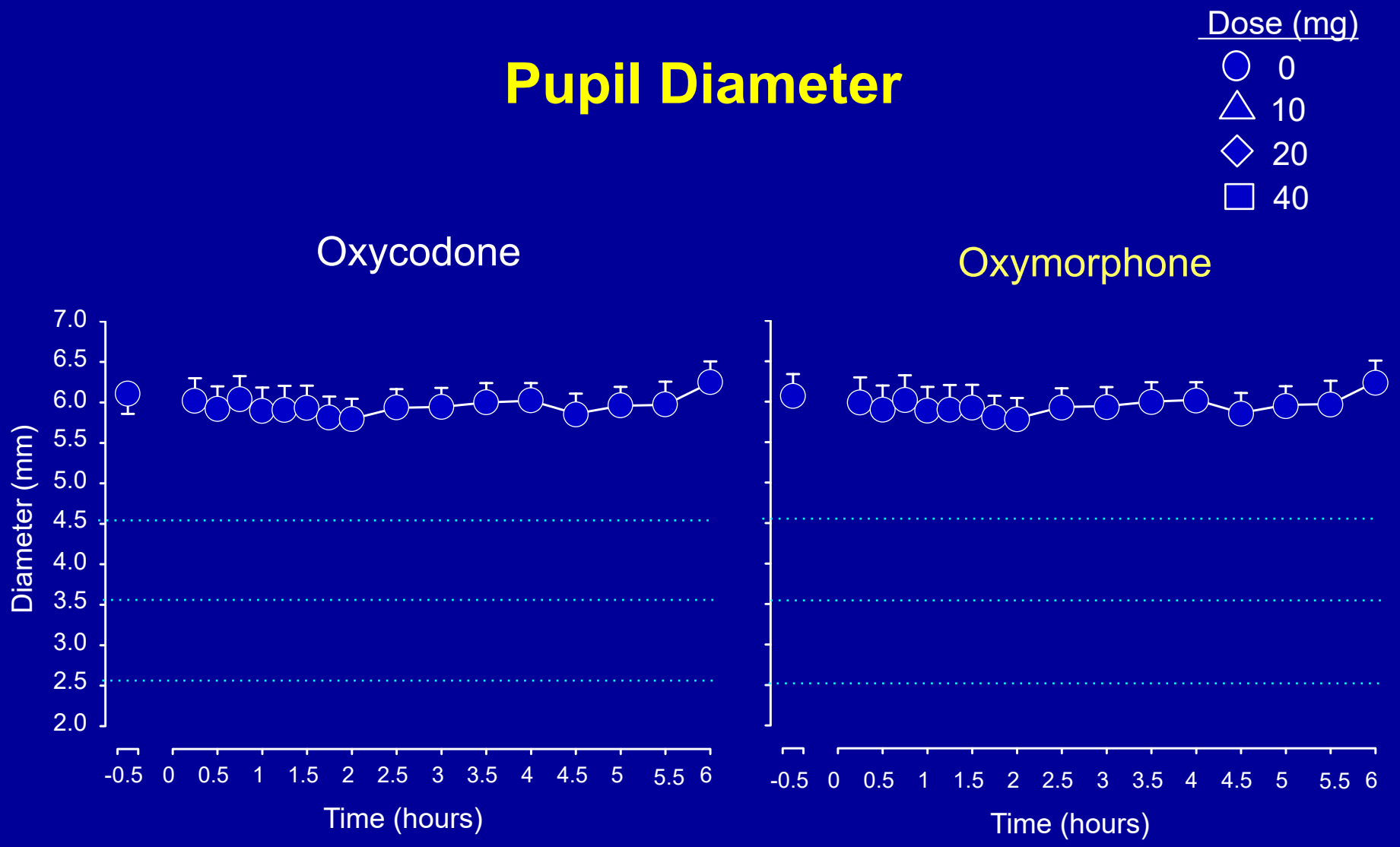
Outcome measures included:

- physiological measures (pupil diameter, end tidal CO_2)
- pain assessments (cold pressor, pressure algometer)
- subjective measures (VAS)
- observer-rated measures (Observer-Rated Agonist Scale)

Relative potency analyses were conducted using the Finney parallel lines bioassay,[6] using a six-point model (3 active doses of each drug)

6. Finney DJ (1964) Statistical method in biological assay. 2nd ed. Hafner: New York.

Pupil Diameter



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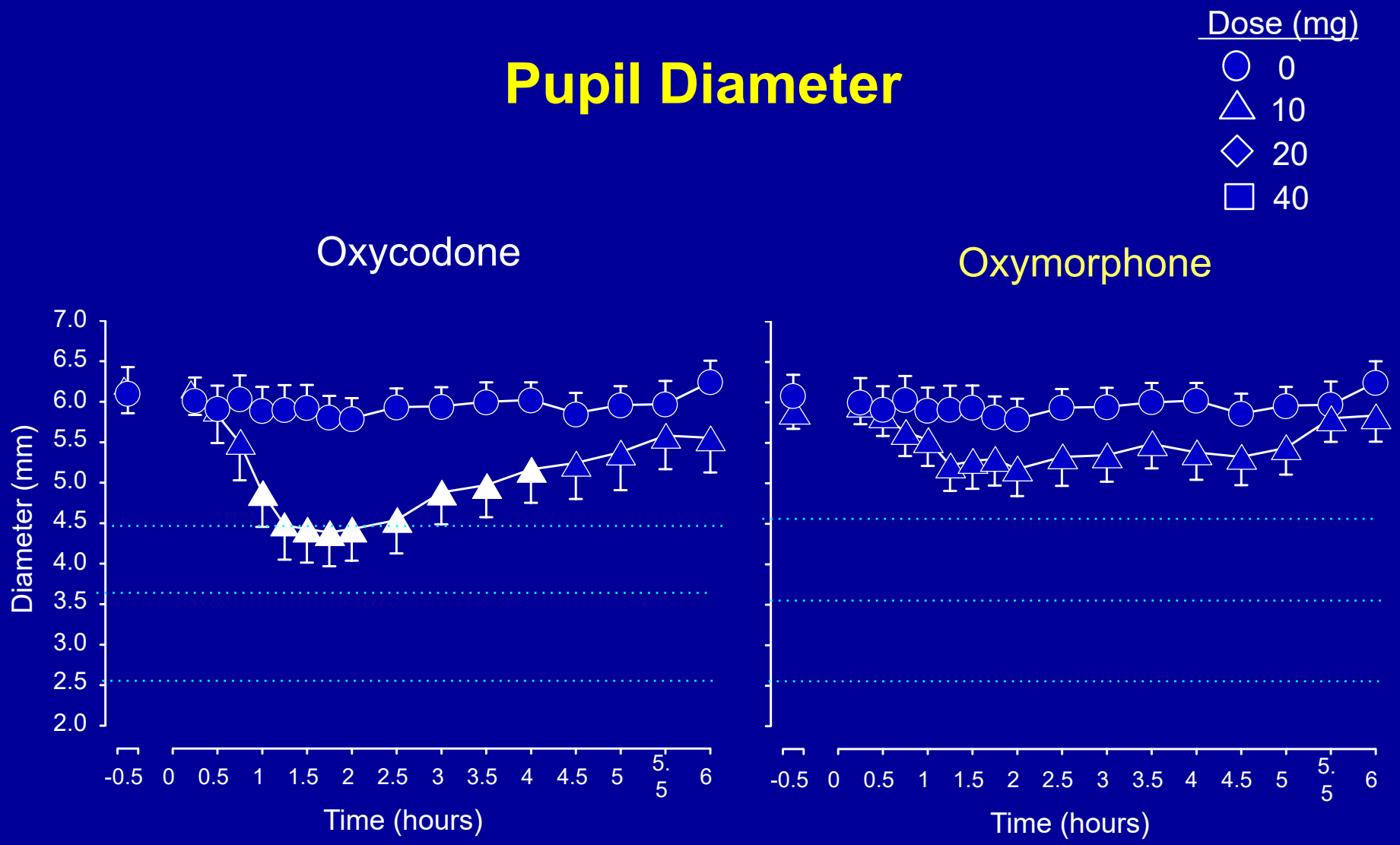

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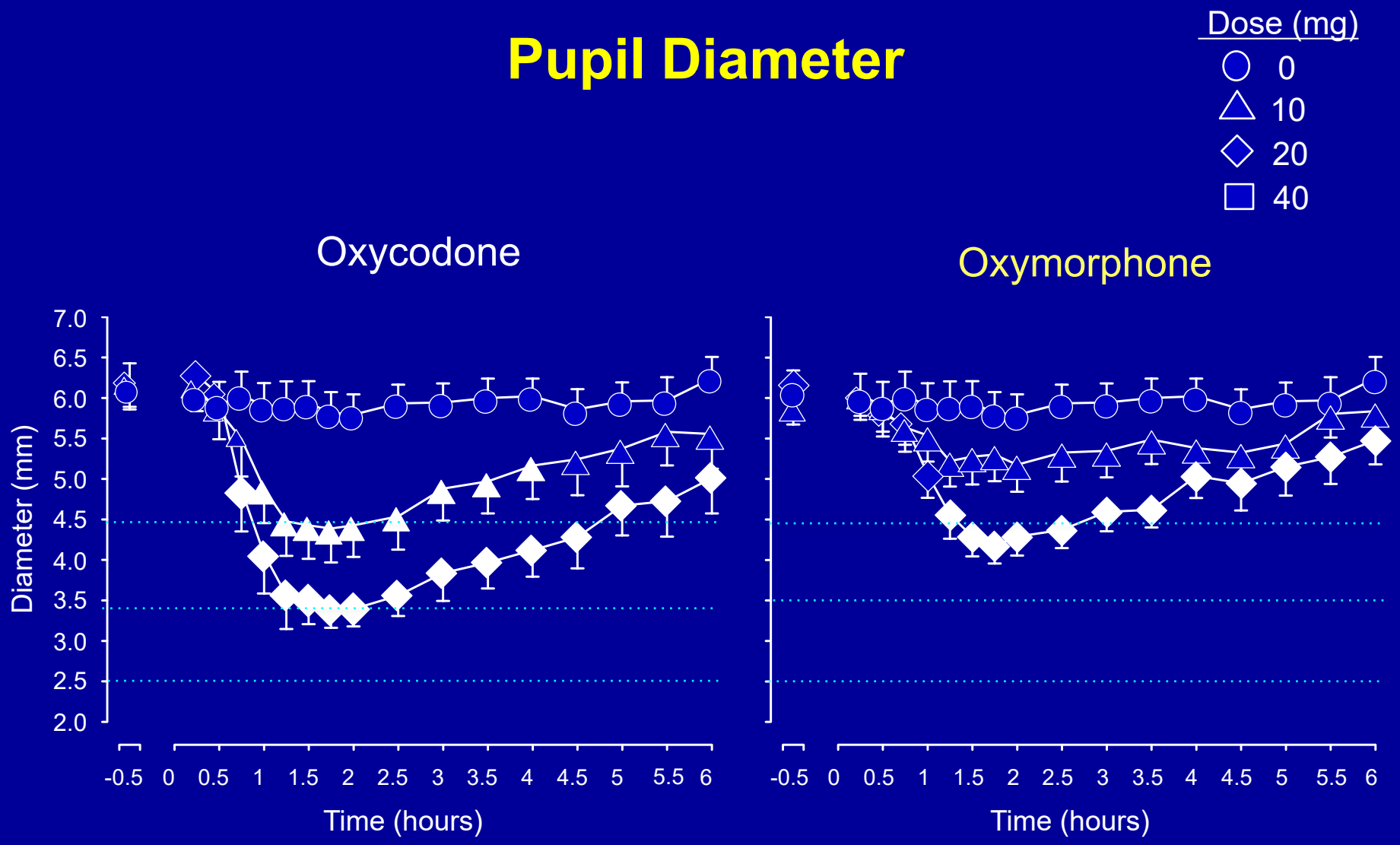

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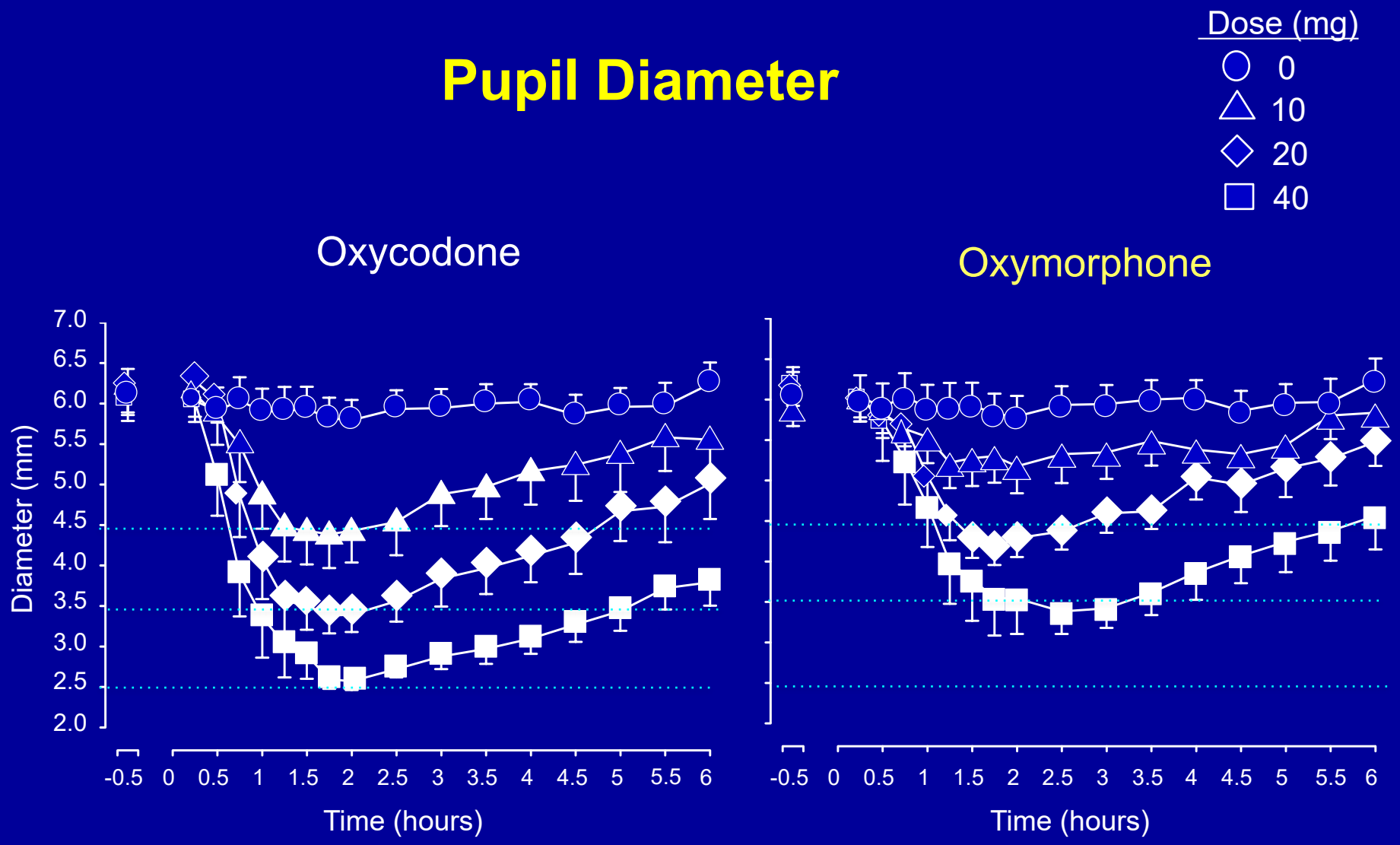
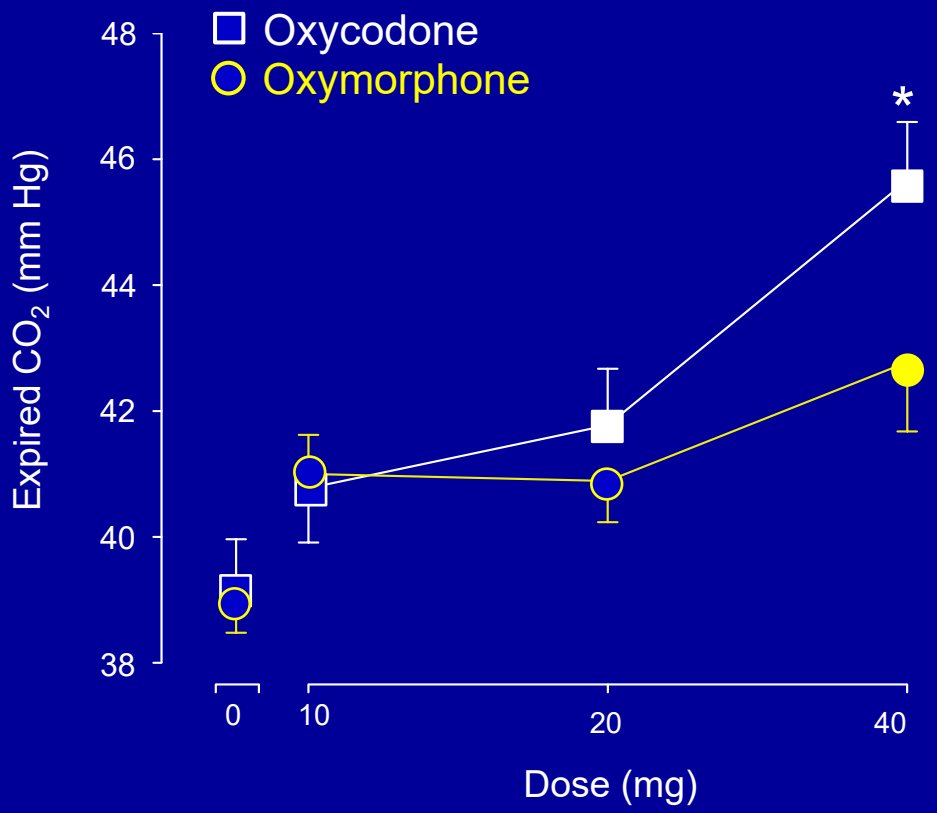


End Tidal CO_2



Pain Assessments

Cold Pressor

- immersed non-dominant into an ice-cold water bath (1.0º C ± 0.5º C)

Pressure Algometer

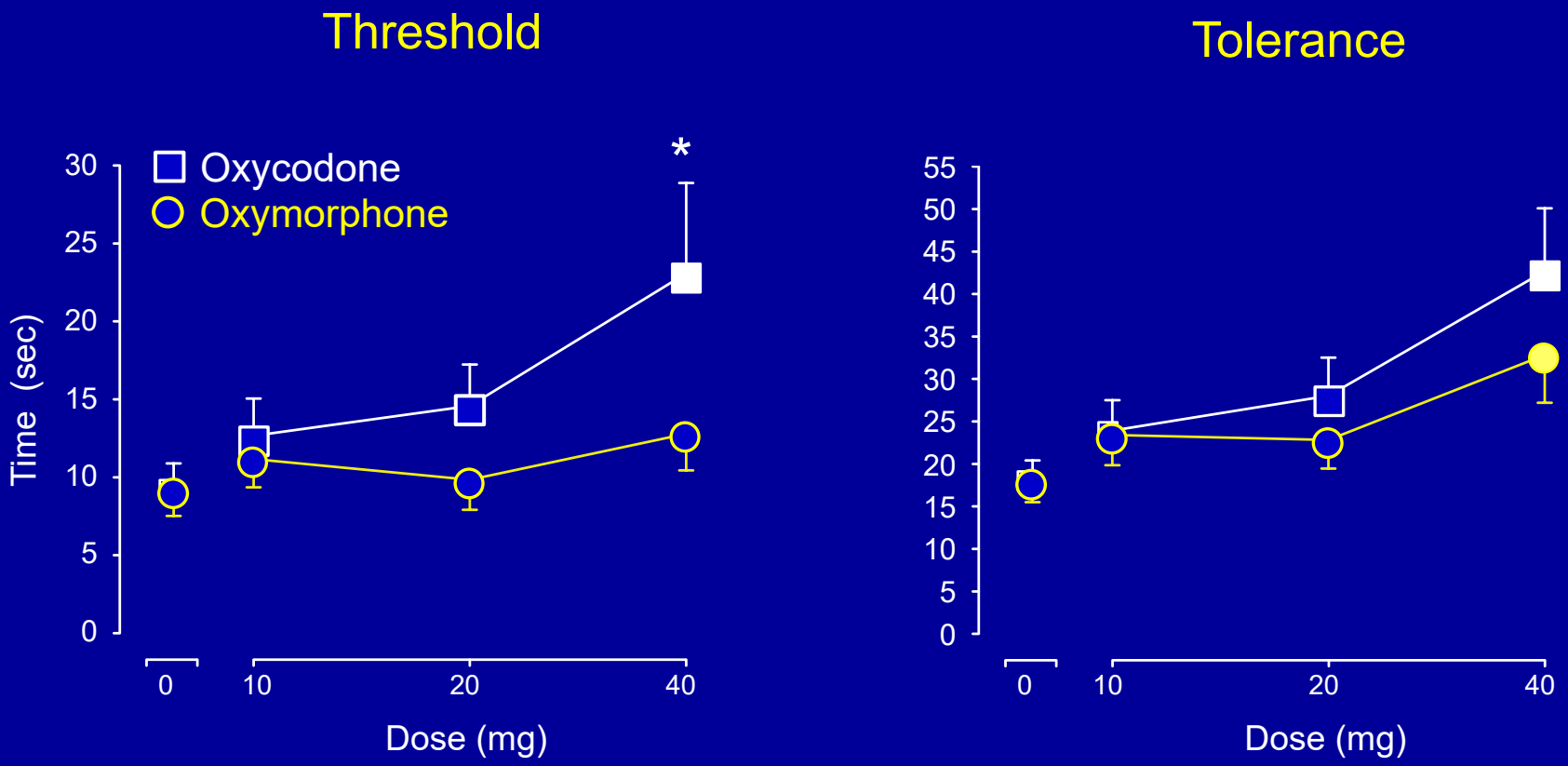
- pressure applied to palm of the dominant hand (40 kPa/sec)

Outcome Measures:

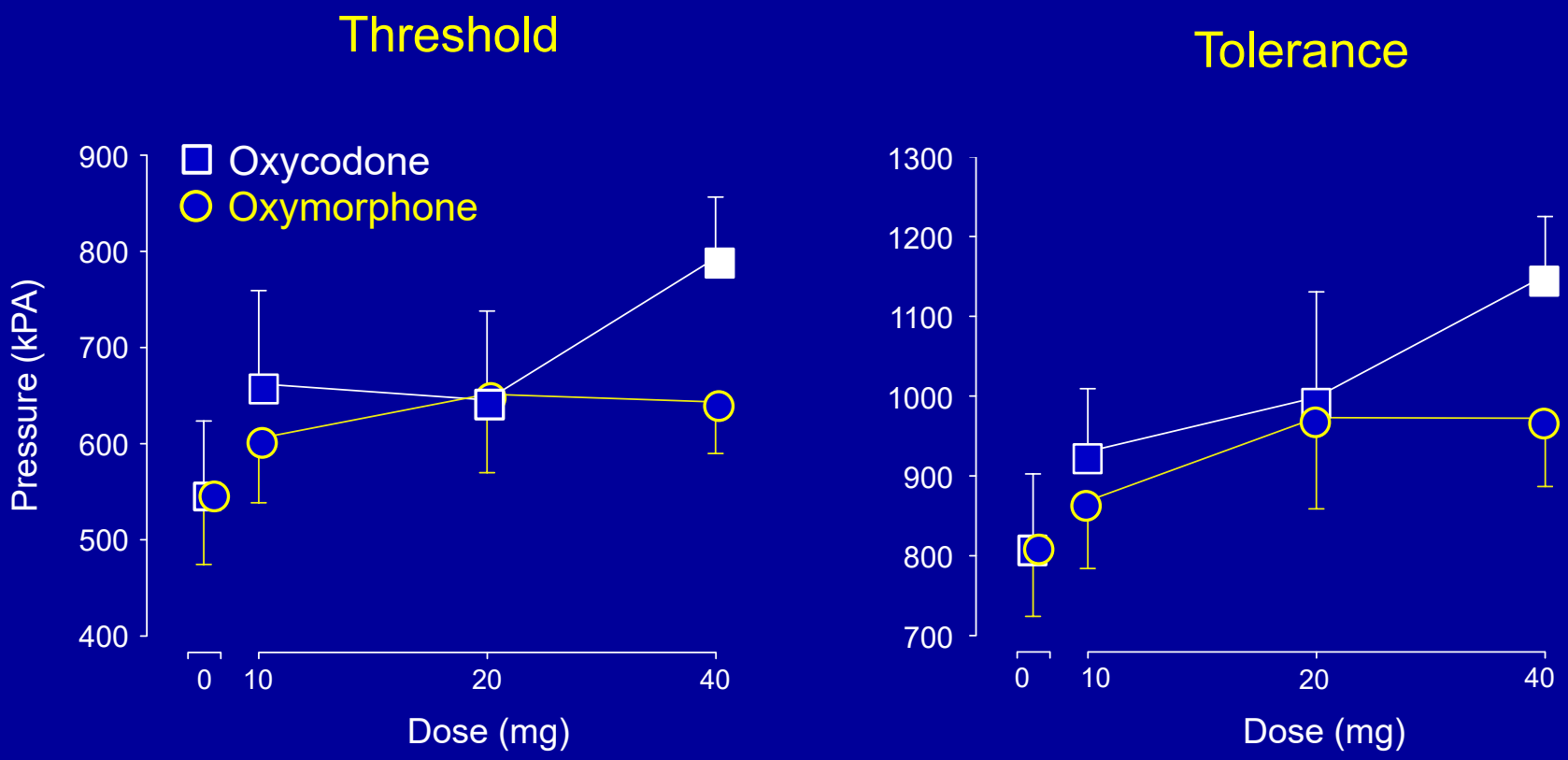
Threshold - point at which pain was detected (sec; kPa)

Tolerance - point at which pain was no longer tolerable (sec; kPa)

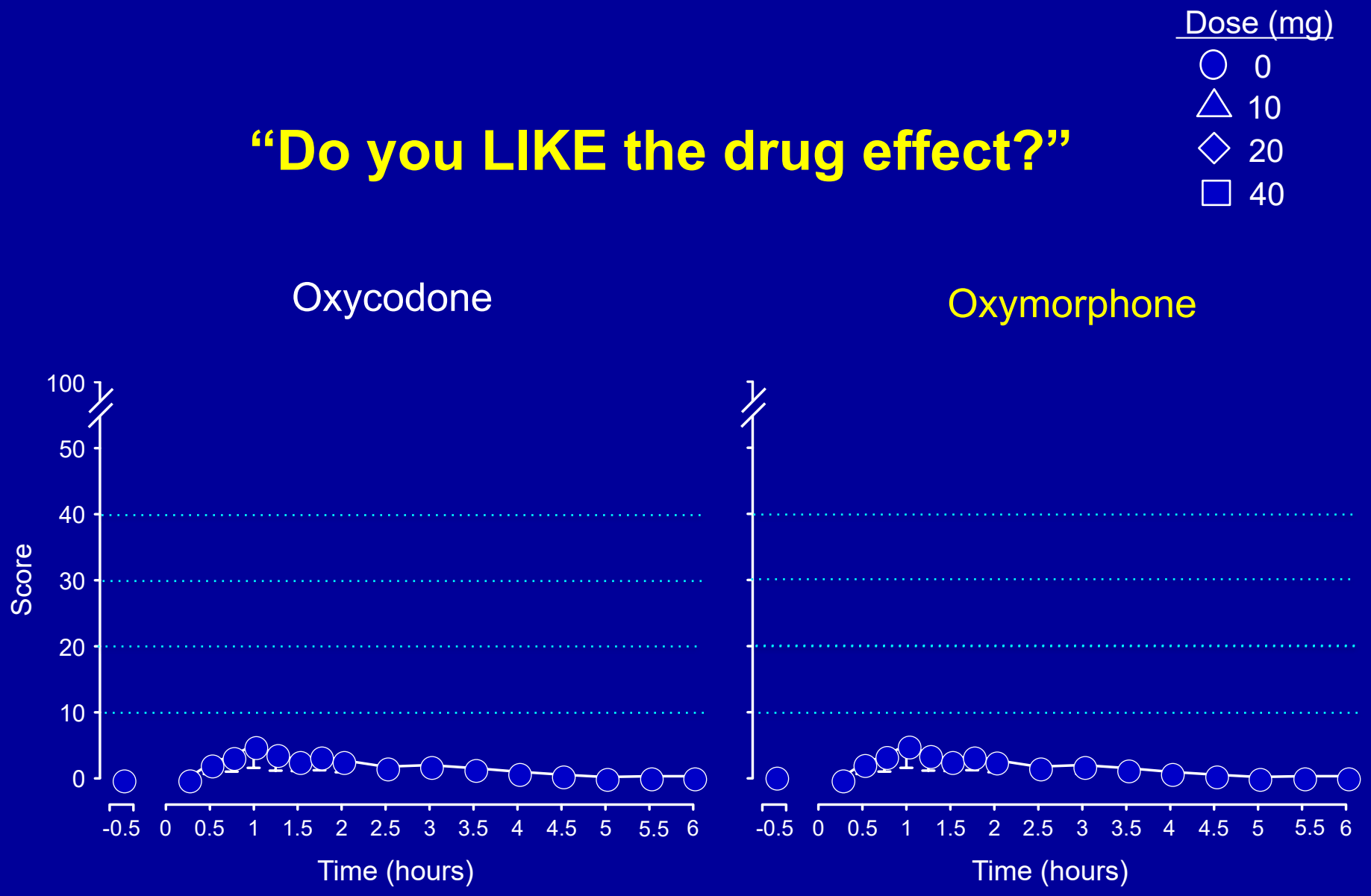
Cold Pressor



Pressure Algometer



“Do you LIKE the drug effect?”



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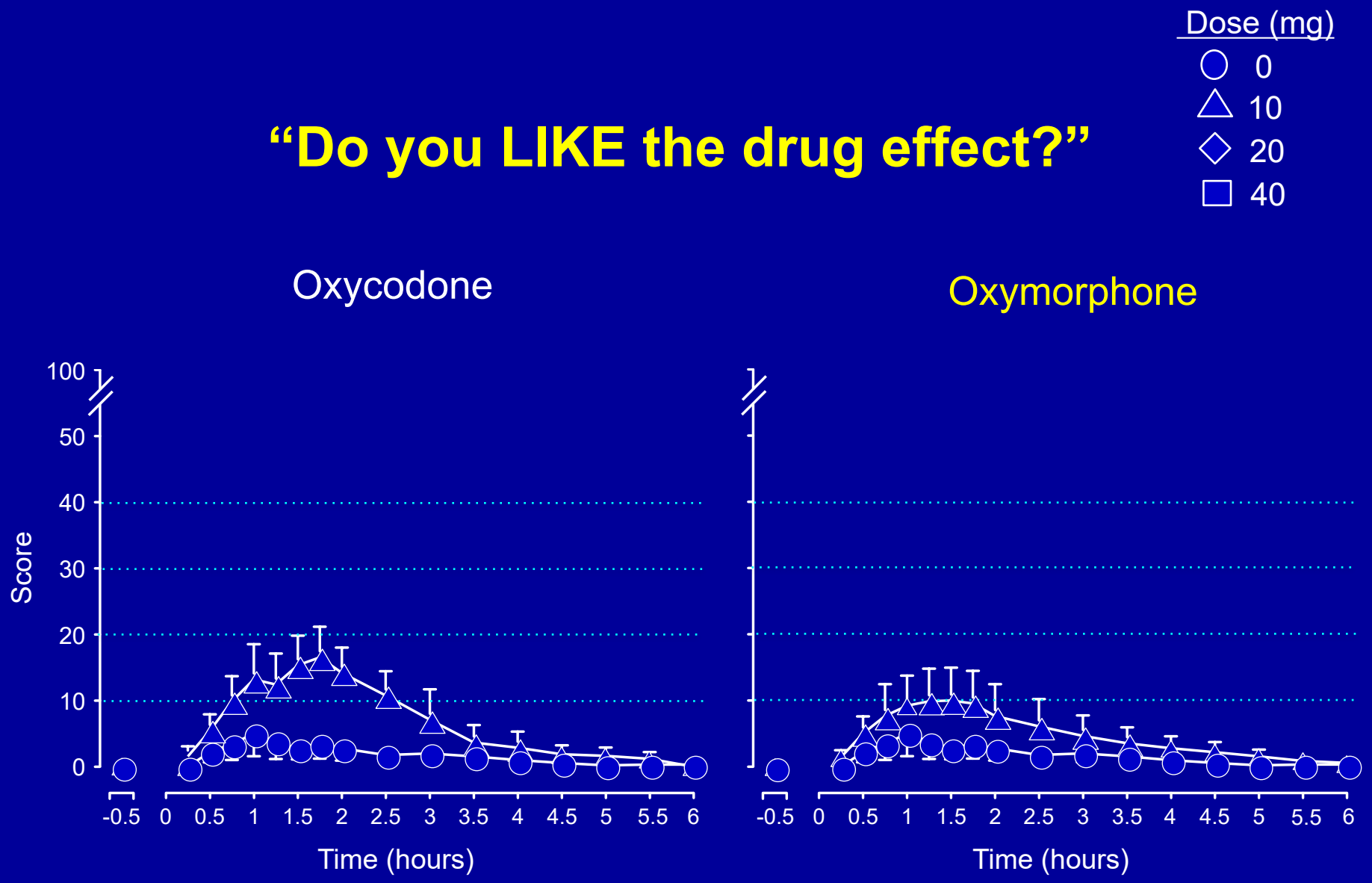

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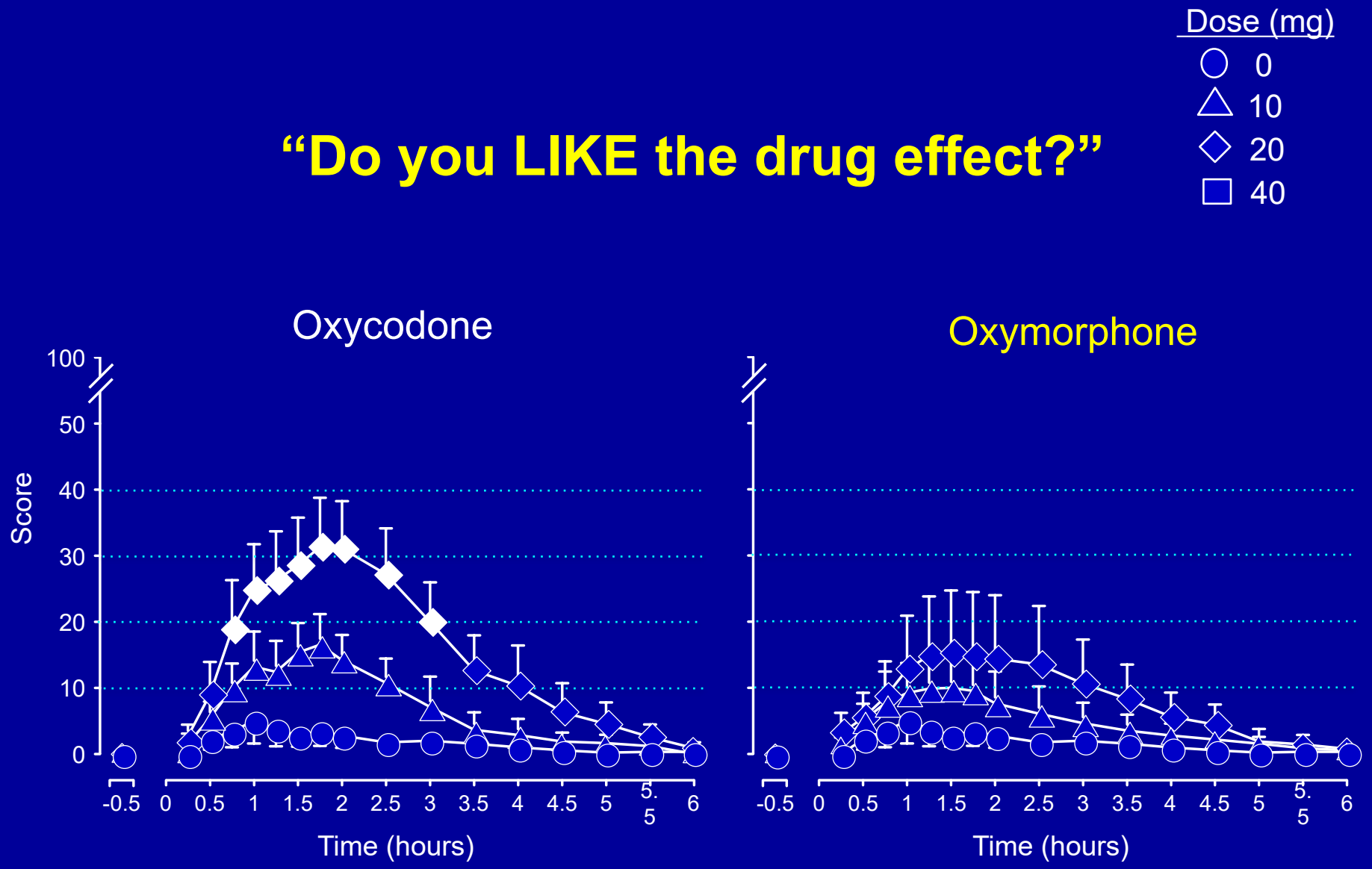

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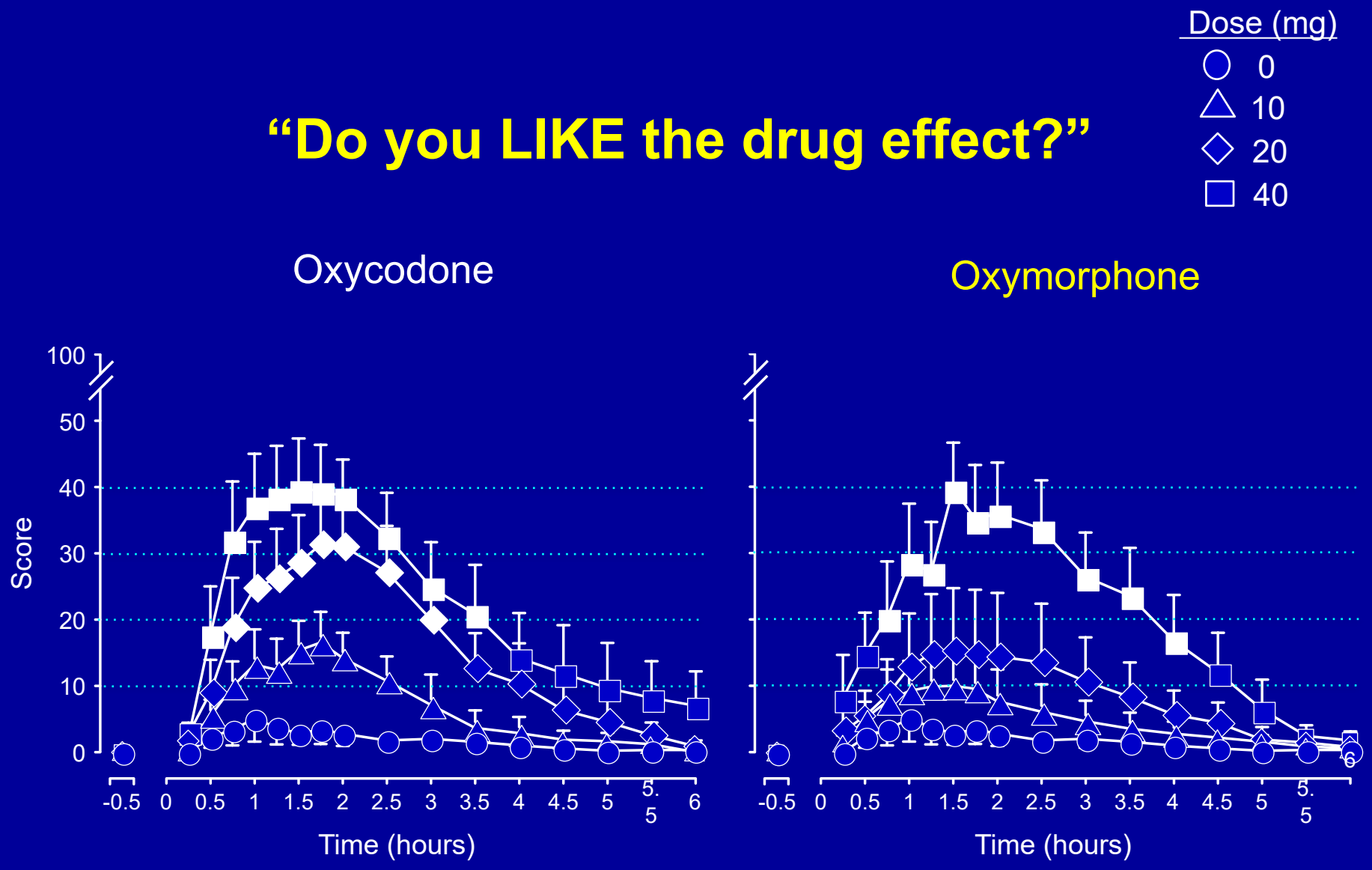
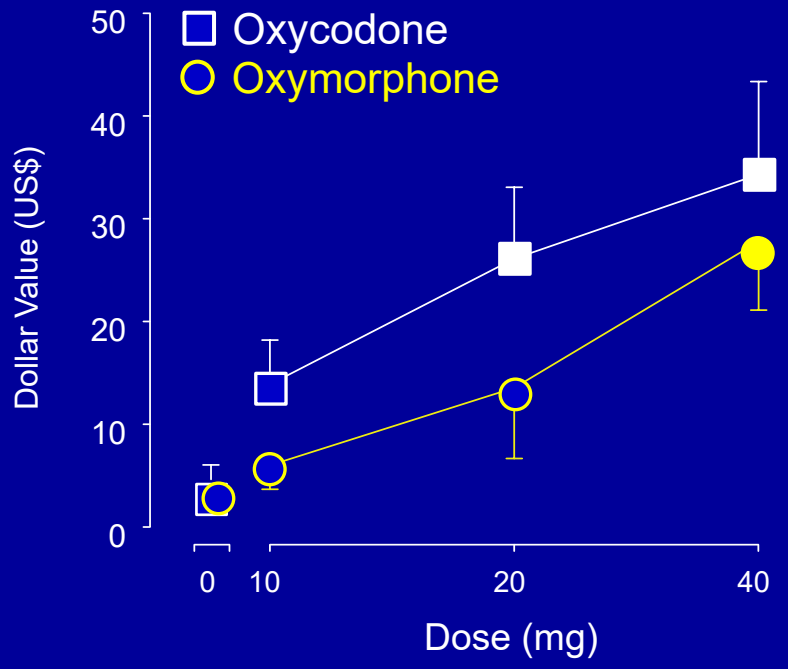
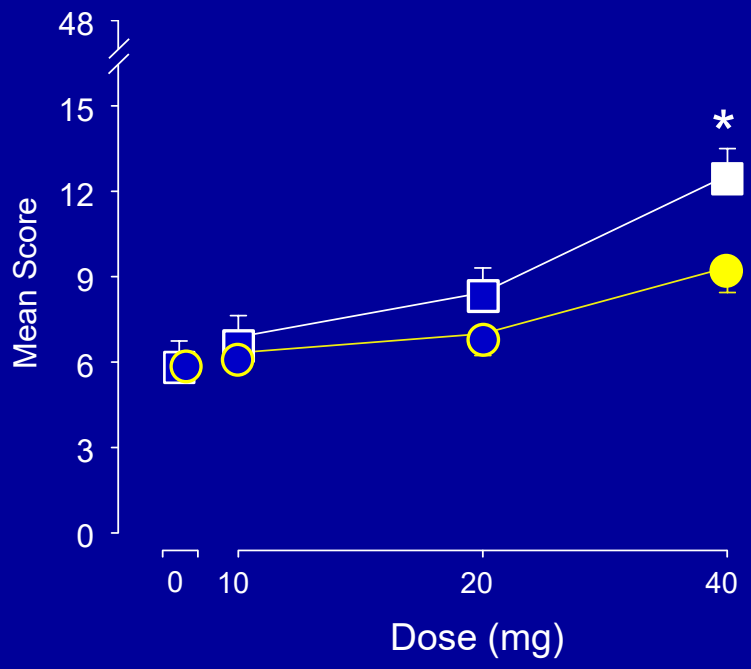


Street Value



Observer Adjectives: Opioid Agonist Scale



Relative Potency Outcomes

Relative potency analyses were conducted on several outcomes, but most were invalid due to substantially greater effects of oxycodone

In general, oxycodone was:

- 2-fold more potent on pain outcomes (e.g., threshold, pressure algometer)
- 1.2-fold more potent on subjective outcomes (e.g., drug liking)

Data are in contrast to the MME tables which suggest than oxymorphone is 2-fold more potent than oxycodone

Results

Oxycodone produced greater effects than oxymorphone on physiological measures (e.g., miosis and end tidal CO_2) at identical doses

Oxycodone produced significant analgesia on measures of tolerance and threshold for both the cold pressor and pressure algometer tests. In contrast, oxymorphone only increased tolerance on the cold pressor

On subject- and observer-rated measures predictive of abuse potential, oxycodone generally produced effects of greater magnitude than identical doses of oxymorphone; however, for some measures, the highest doses appeared equivalent

Conclusions

The present study suggests that oral oxymorphone is actually less potent than oxycodone on a broad array of measures, including experimental pain outcomes

These findings are in direct conflict with the published potency ratios for oxymorphone derived from clinical pain studies

One contributing factor is the low bioavailability of oral oxymorphone (10%) compared to oxycodone (60-87%); however, at high doses, abuse potential was similar to oxycodone

If one accepts the analgesic potency estimates from clinical trials as accurate, it may be that these are not predictive of relative potency for other pharmacodynamic actions

However, if experimentally-induced pain is a valid assay for analgesia, then oxymorphone may have greater abuse liability than oxycodone at equianalgesic doses

In order to fully characterize the relative abuse liability of oxymorphone, a broader range of doses/routes of administration need to be examined

Relative Potency of Oxymorphone

Two placebo-controlled studies conducted to examine:

1) Relative abuse potential and relative potency of oral oxymorphone

2) Relative abuse potential and relative potency of *intravenous* oxymorphone

Background

In the 1970s, prior to the initial removal of oral oxymorphone from the U.S .market, there were documented cases of opioid users injecting oxymorphone, with some preferring it over heroin[2]

Since the re-introduction of oxymorphone products onto the US market in 2006, oxymorphone has been misused via IV route, at a disproportionately high rate compared to other rx opioids

IV oxymorphone has been associated with significant public health harms:

- HIV outbreak in rural Indiana (88% of infected individuals)[7]
- acute kidney injury[8]
- blood vessel and blood clotting disorders[9,10]

2. Watkins TD, Chambers CD (1972) Oxymorphone Abuse Among Current Narcotic Addicts pp. 307-312.
7. Peters PJ et al. (2016) HIV infection linked to injection use of oxymorphone in Indiana, 2014–2015. NEJM 375(3):229-39
8. Bonnecaze et al (2018). Acute kidney injury is common with intravenous abuse of extended-release oral oxymorphone. *Nephrology (Carlton)* 8;23(10):921-926.
9. Amjad & Parikh (2013). Opana-ER Used the Wrong Way: Intravenous Abuse Leading to Microangiopathic Hemolysis and a TTP-like Syndrome; Blood, 122(20):3403.
10. Kotbi et al (2015); Opana(®) ER Induced Thrombotic Thrombocytopenic Purpura Int Med Case Rep J. 2015 Apr 29;8:97-8

Background

Due to these safety concerns, the FDA requested the removal of Opana® ER from the market in 2017

However, generic formulations of both immediate- and extended-release products remain on the market

No controlled data are available on the abuse potential of IV oxymorphone

Aims

Primary aims of this dose-finding, double-blind, placebo-controlled, two-site study:

1)Compare IV oxymorphone to IV morphine, oxycodone and hydromorphone on an array of abuse potential, physiological and observer-rated effects

2)Calculate the relative potency of IV oxymorphone on abuse potential and safety/physiological outcomes

This study also served as a pilot study to identify equieffective doses of oxymorphone, comparator opioids for a subsequent study on IV oxymorphone self-administration (currently in progress)

Methods

Two-site, within subject, double-blind, placebo-controlled, 5-week inpatient study

19 experimental sessions were conducted, one IV dose administered per session

Data collected before and for 6 hrs after IV dose administration

Sessions were conducted up to 5 days per week

Participants

Participants were otherwise healthy adults (ages 18-55) with moderate-to-severe opioid use disorder, physical dependence and current IV use

6 participants were included in the data analysis:

1 woman, 5 men

1 African American, 5 Caucasian

Age: 33 (± 3.4) years

BMI: 22 (± 1.5) kg/m^2

Participants

Tobacco: all were daily cigarette smokers

Intravenous heroin/fentanyl: 29 (± 0.5) days of use in past 30 days

Other past 30-day drug use:

- alcohol (n=2)
- rx opioid (n=3)
- cocaine (n=4)
- benzodiazepine (n=1)
- methamphetamine (n=1)

Doses

Participants were stabilized on oral morphine (30 mg, qid)

During each experimental session, one IV dose was administered (mg/70 kg):

oxymorphone (1.8, 3.2, 5.6, 10, 18, 32)

hydromorphone (1.8, 3.2, 5.6, 10, 18)

oxycodone (18, 32, 56)

morphine (18, 32)

placebo

Dose selection: wide range of oxymorphone doses selected; previous studies included 18 mg hydromorphone, 50 mg oxycodone and morphine;[9,10] MME tables indicated IV oxymorphone : IV morphine = 1:10

Oxymorphone (56 mg/70 kg) and morphine (56 mg/70kg) were withheld on several occasions due to safety concerns (e.g., sedation); data not presented here

Doses of each drug were administered in ascending order for safety but were otherwise randomized

9. Comer SD et al (2008) Abuse liability of prescription opioids compared to heroin in morphine-maintained heroin abusers. Neuropsychopharmacology 33: 1179-91.
10. Walsh SL et al (2017) Effect of buprenorphine weekly depot (CAM2038) and hydromorphone blockade in individuals with opioid use disorder: a randomized clinical trial. JAMA Psychiatry 74: 894-902.

Measures

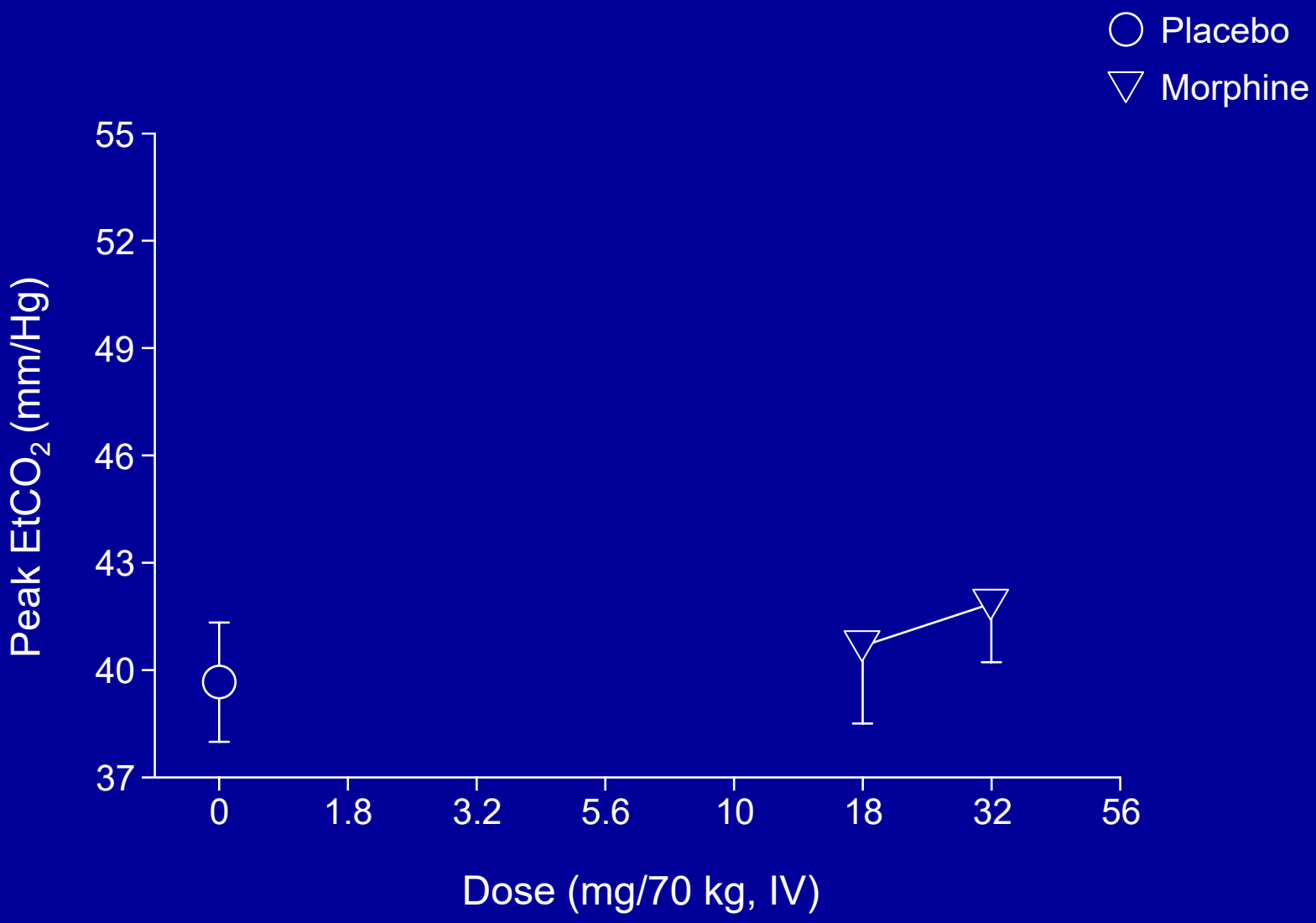
Primary outcomes:

- safety/physiological outcomes (O_2 saturation, $EtCO_2$, respiration rate, pupil diameter)
- subjective measures of drug effect (VAS ratings of drug liking, street value)

Relative potency analyses were conducted using the Finney parallel lines bioassay,[6] using a six-point model (3 active doses of each drug)

6. Finney DJ (1964) *Statistical method in biological assay*. 2nd ed. Hafner: New York.

End Tidal CO_2



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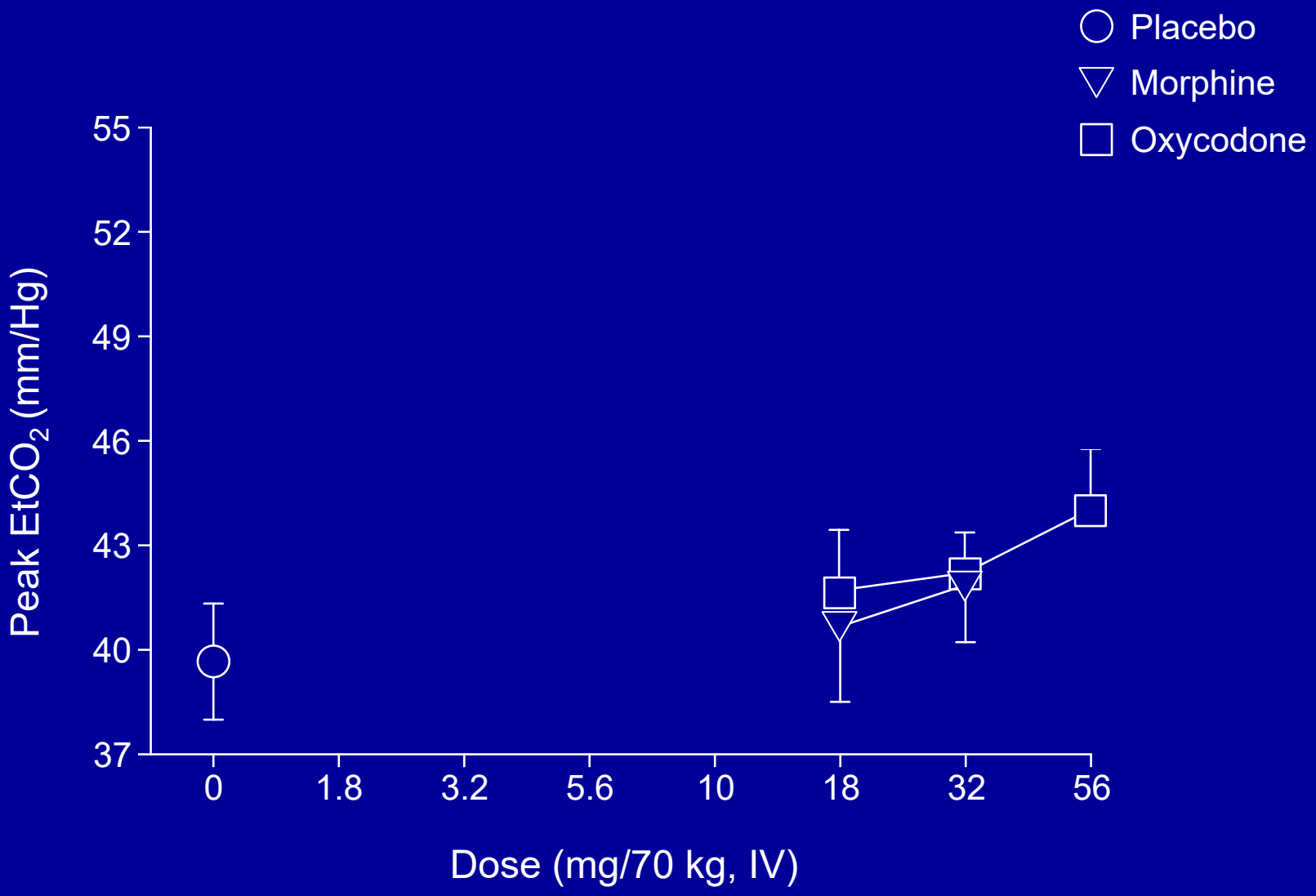

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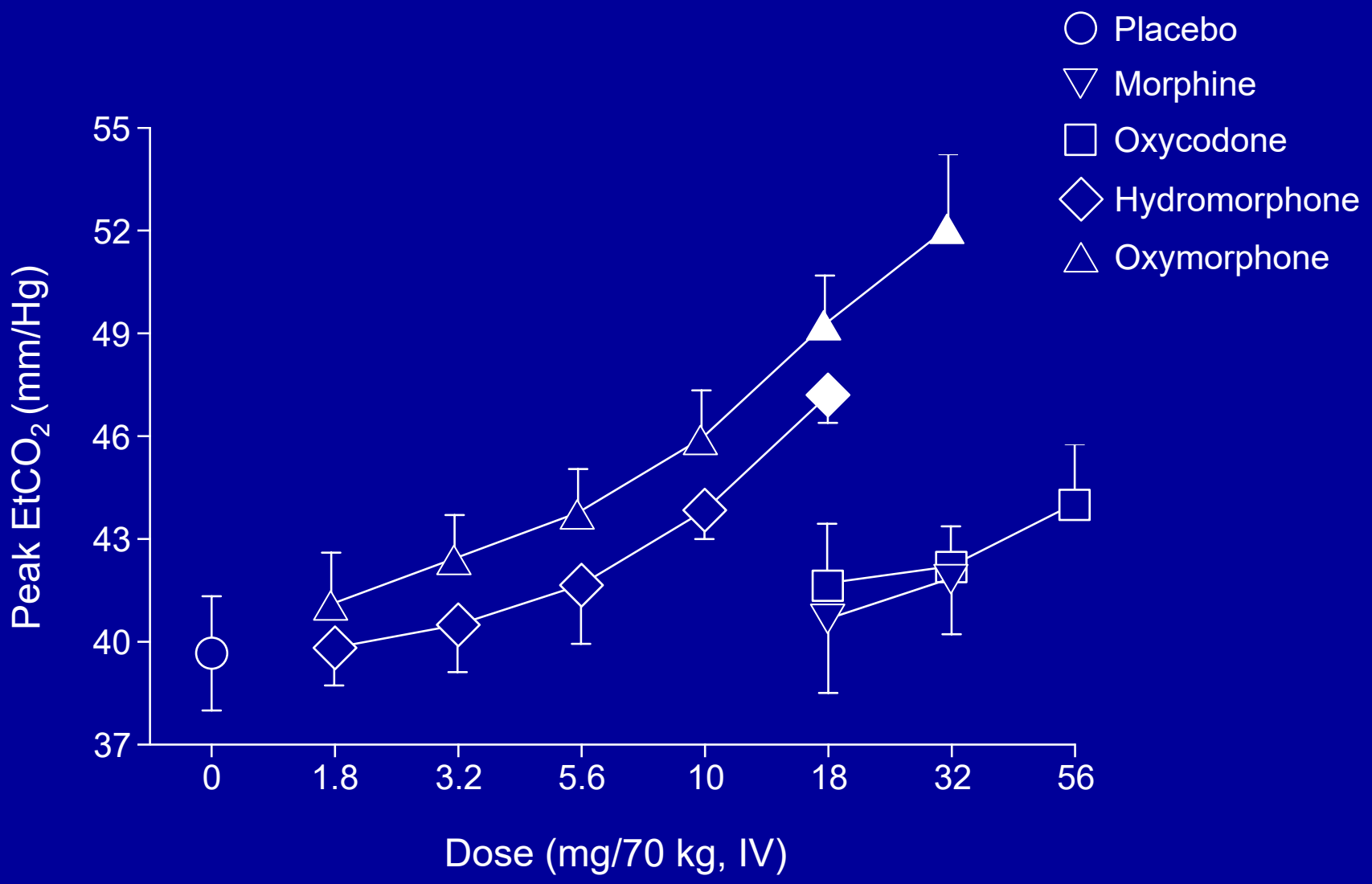
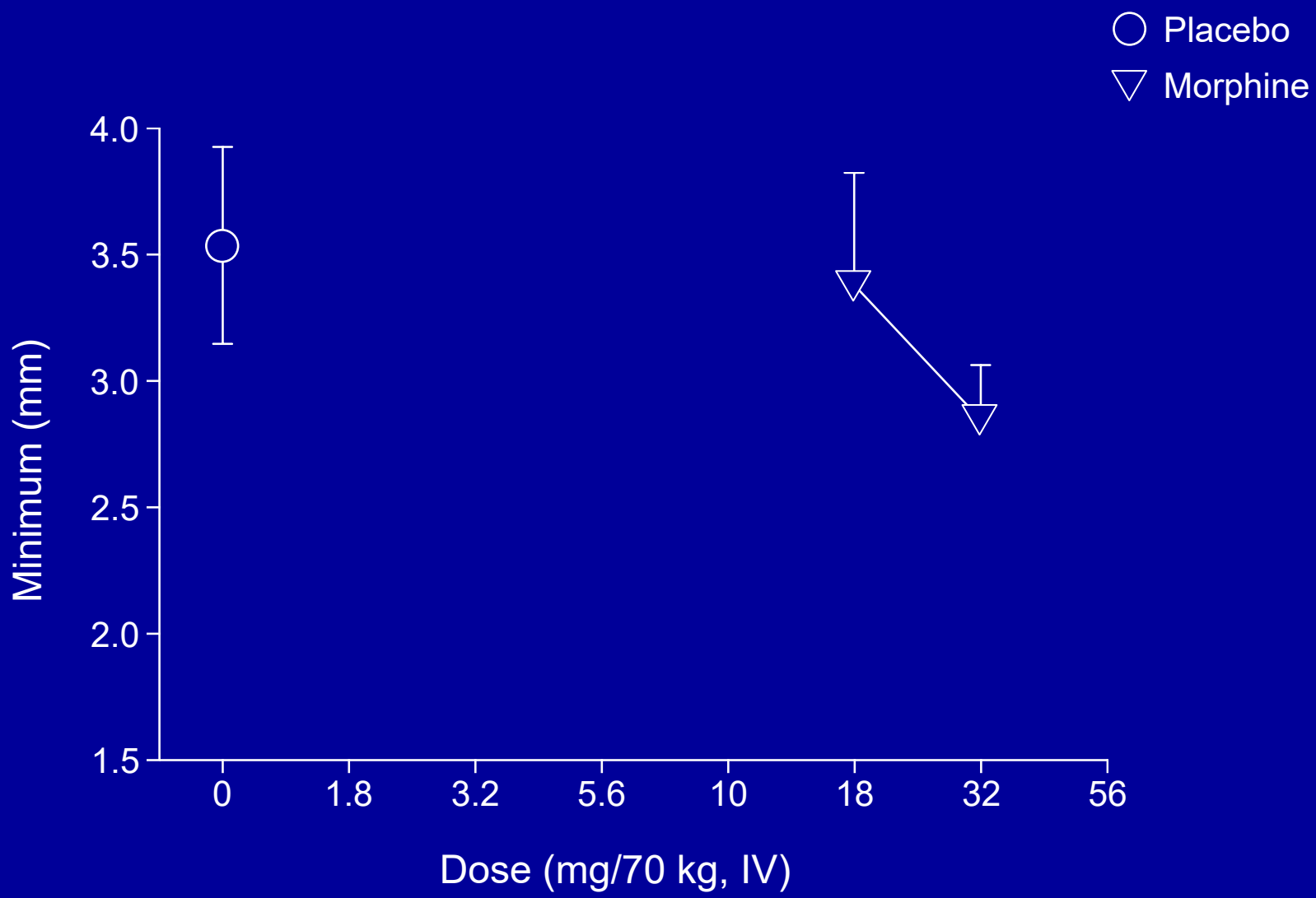


Pupil Diameter



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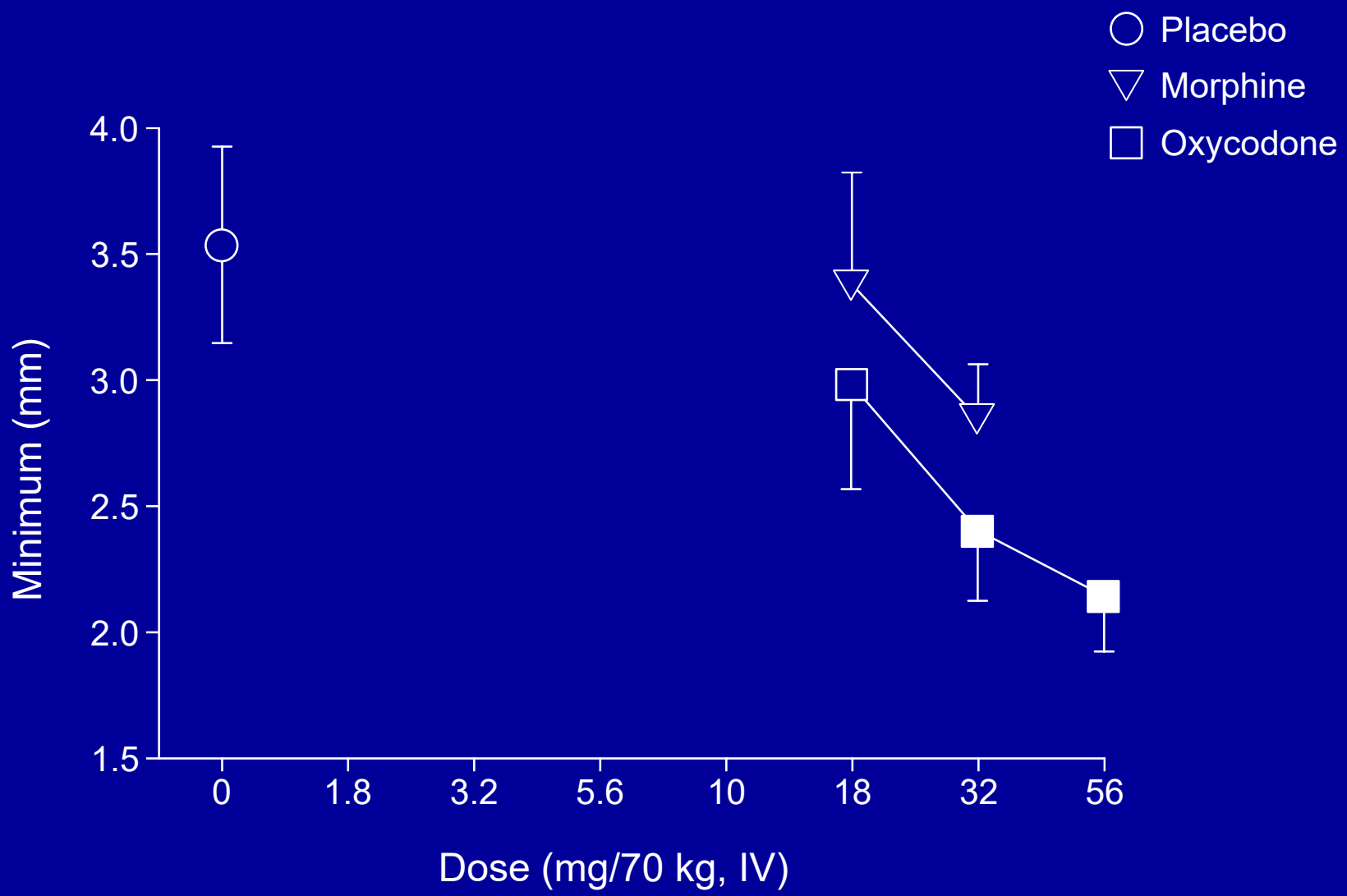

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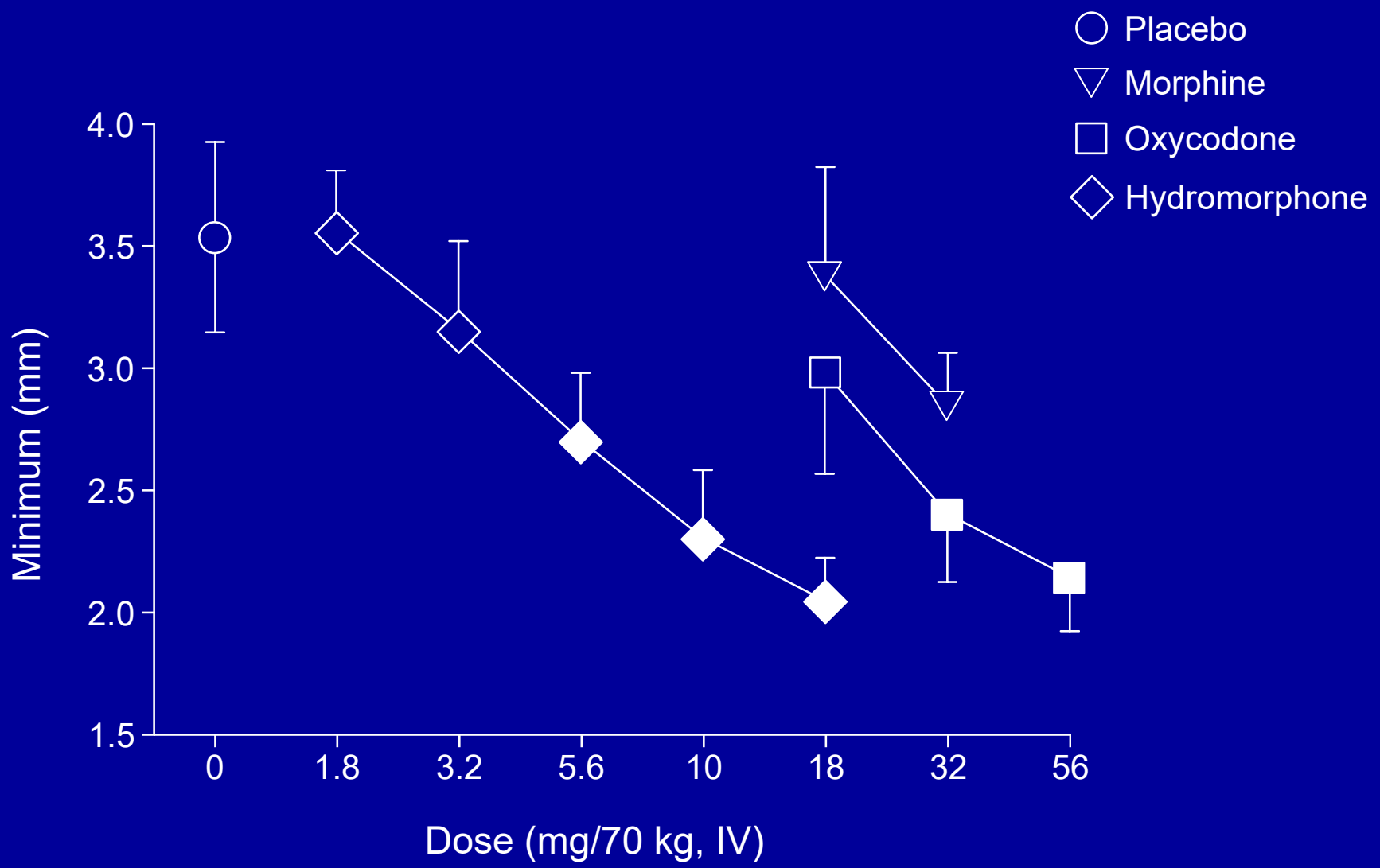

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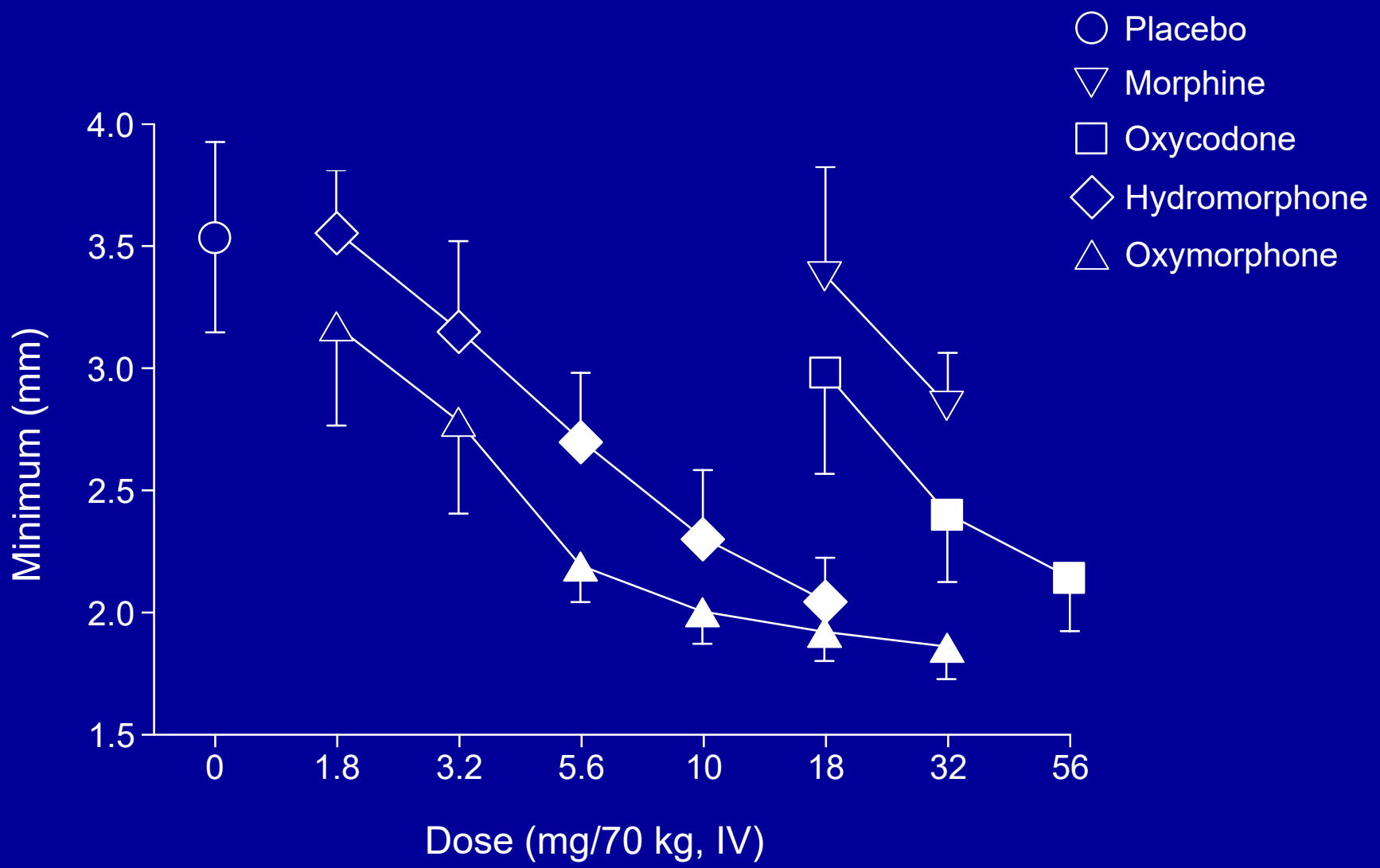

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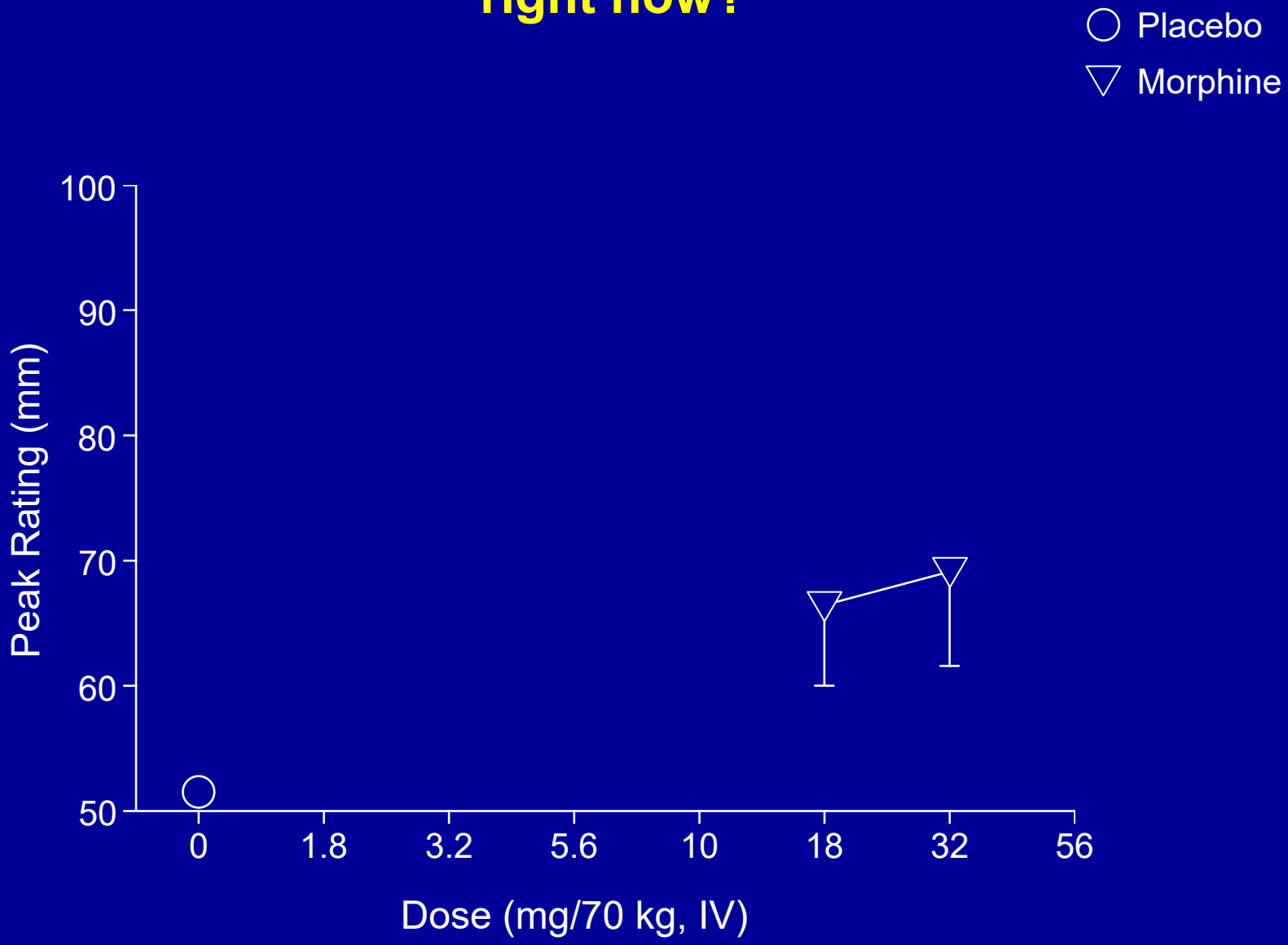

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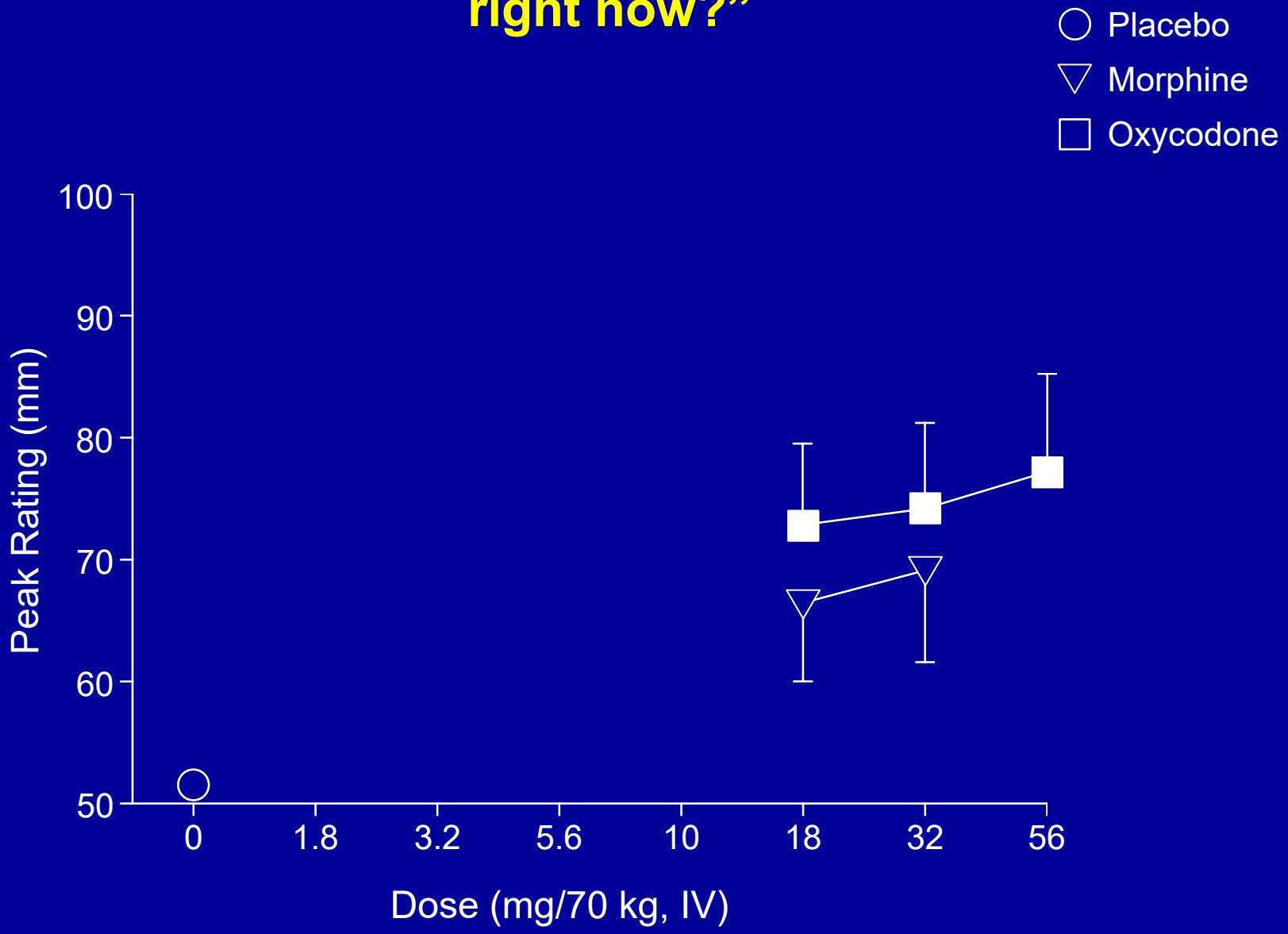

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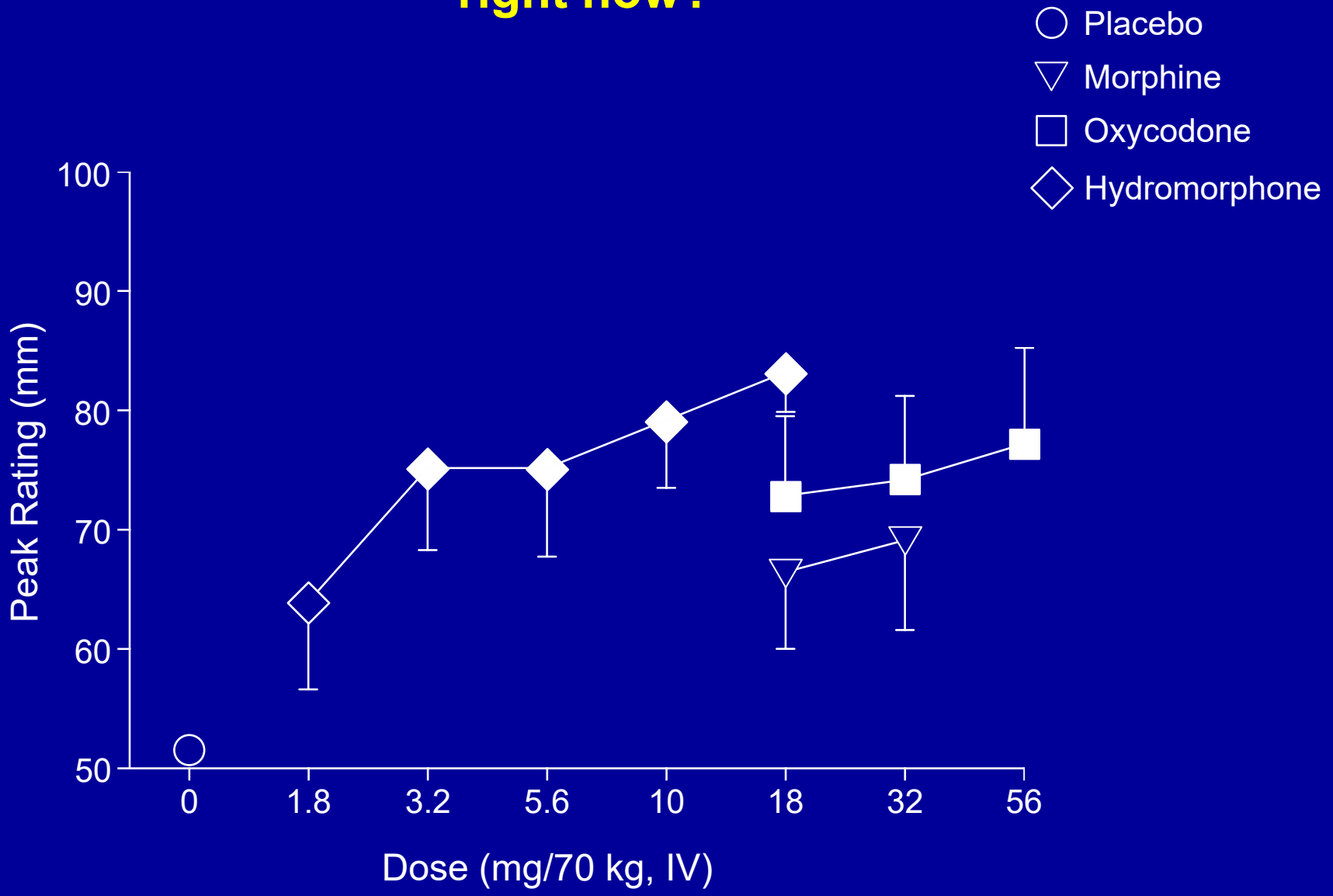

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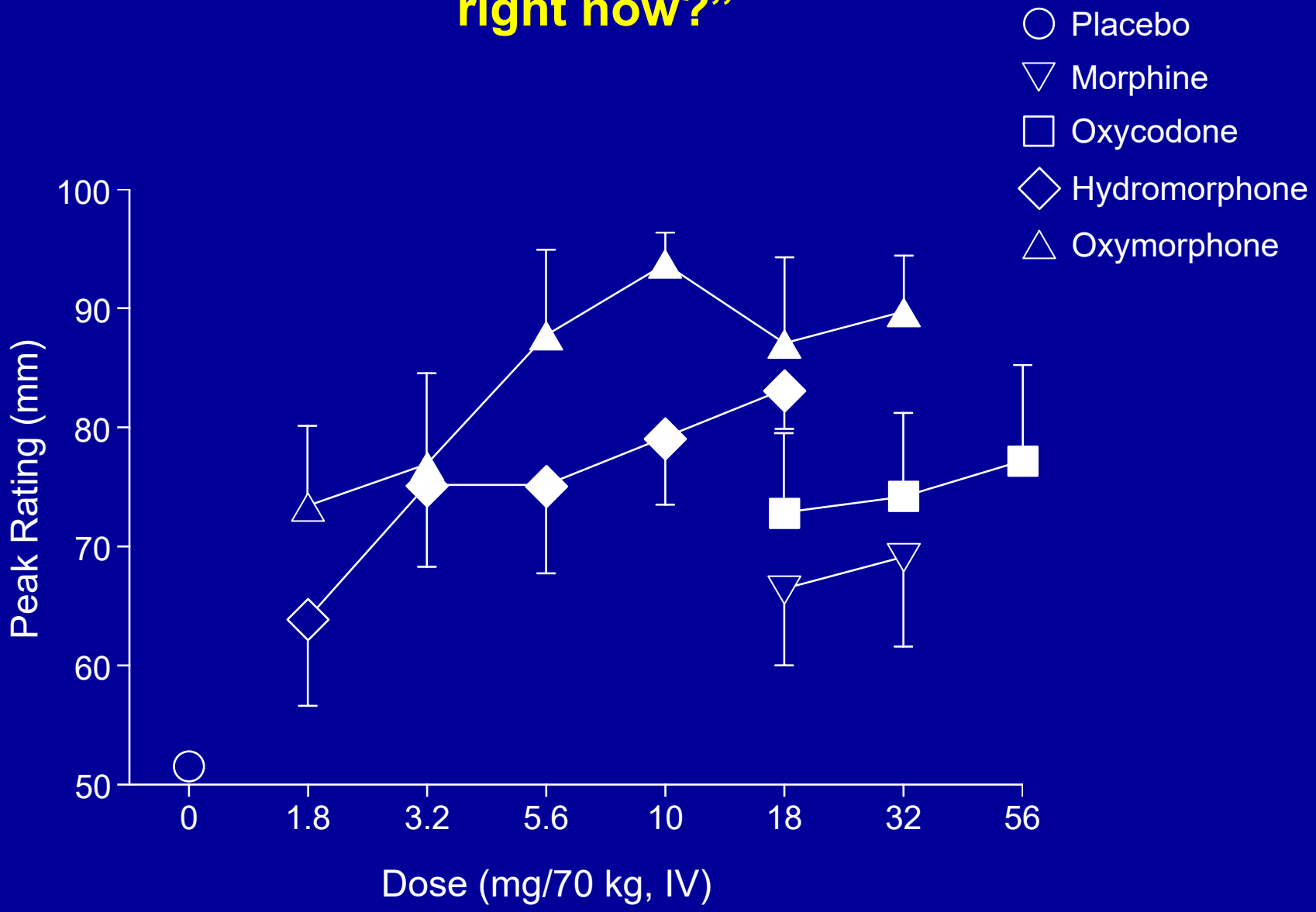
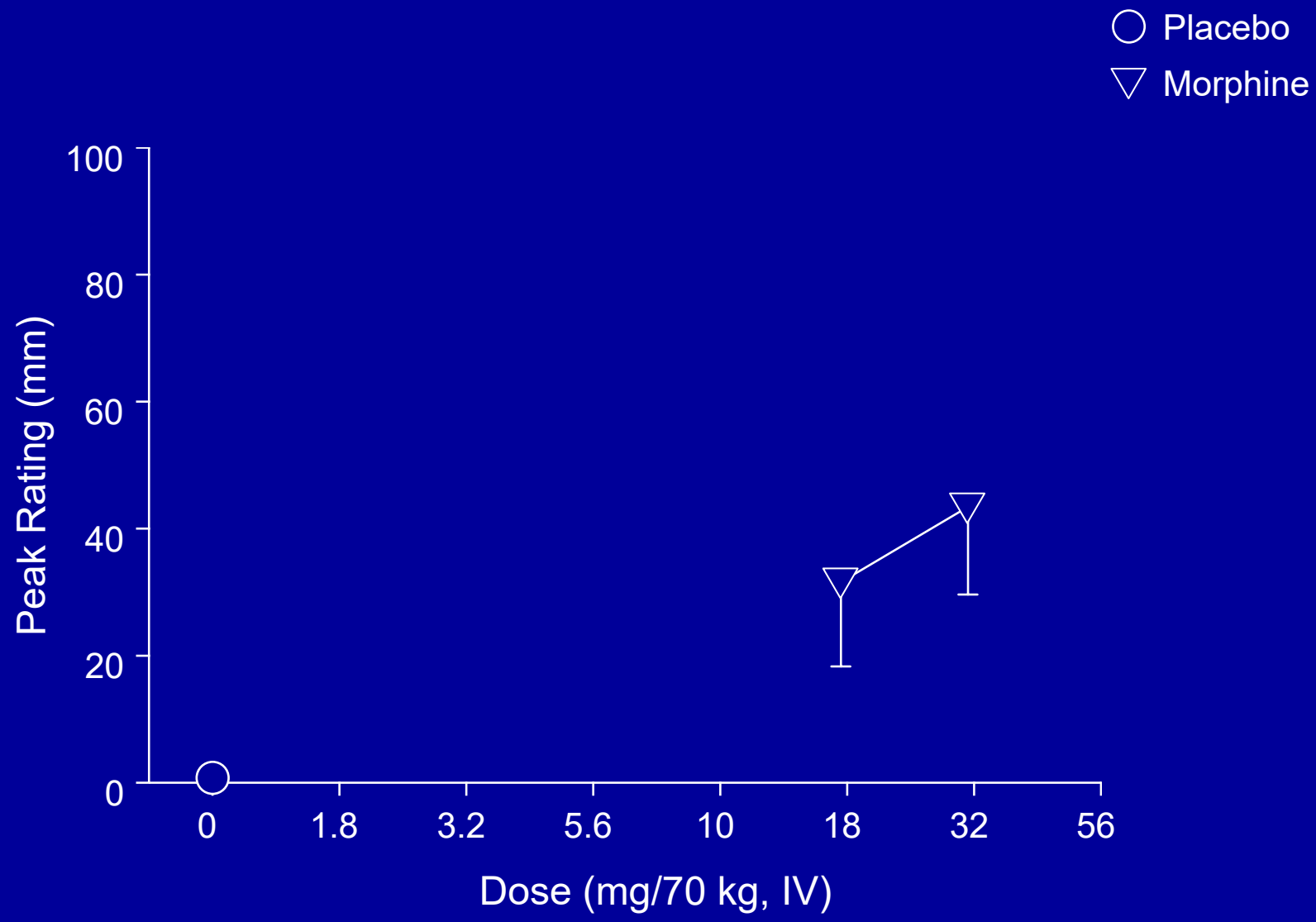


“Do you feel High?”



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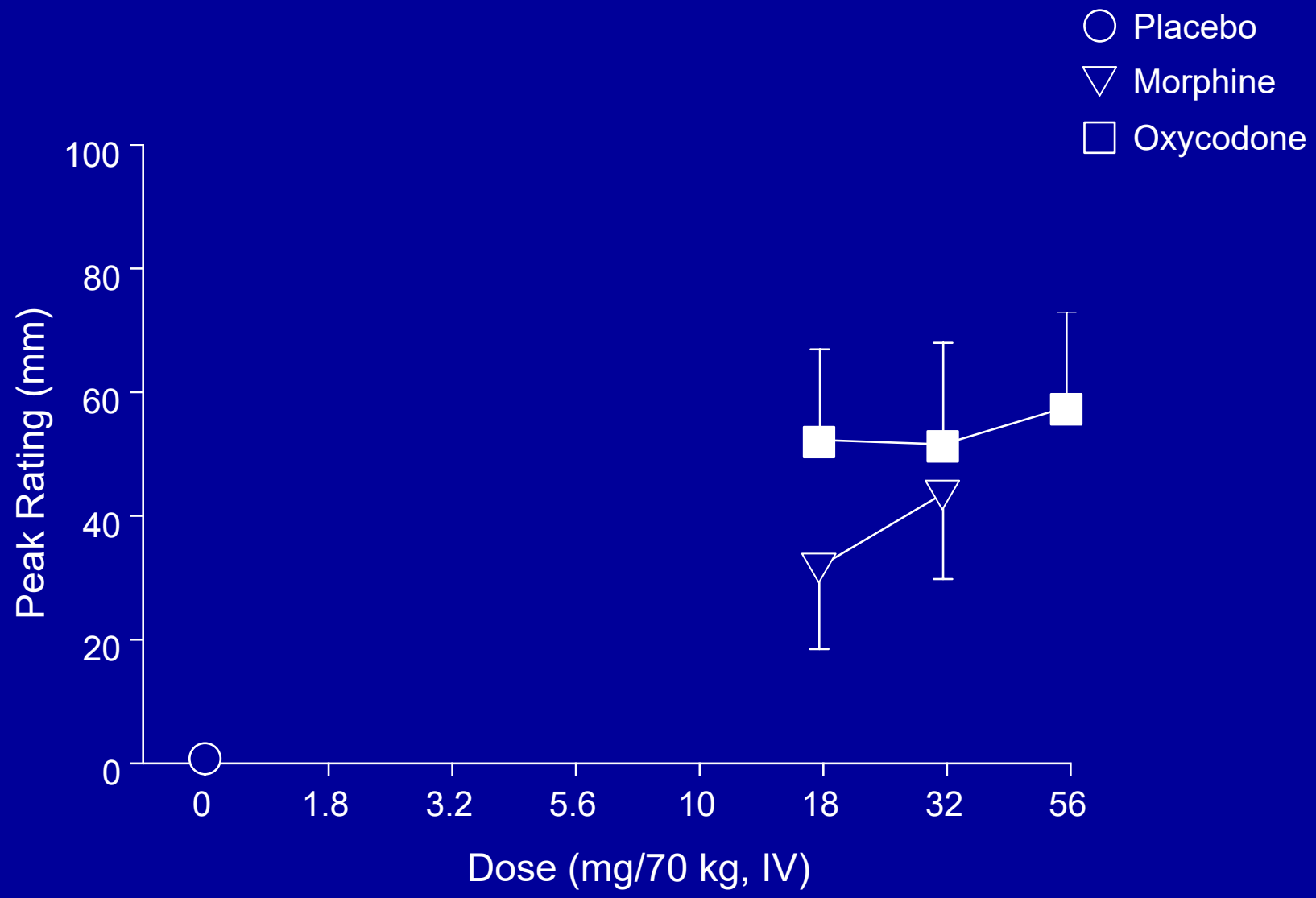

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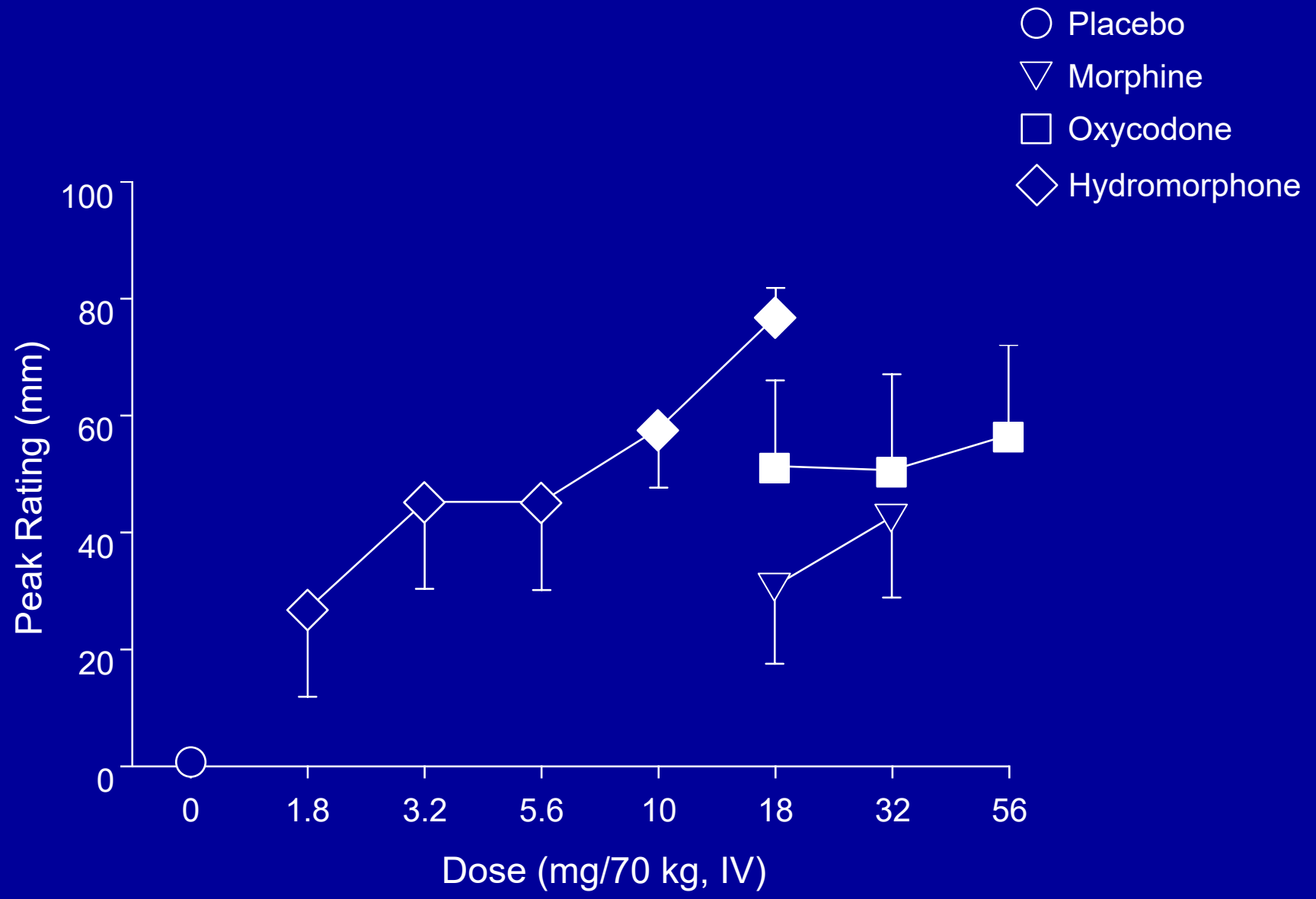

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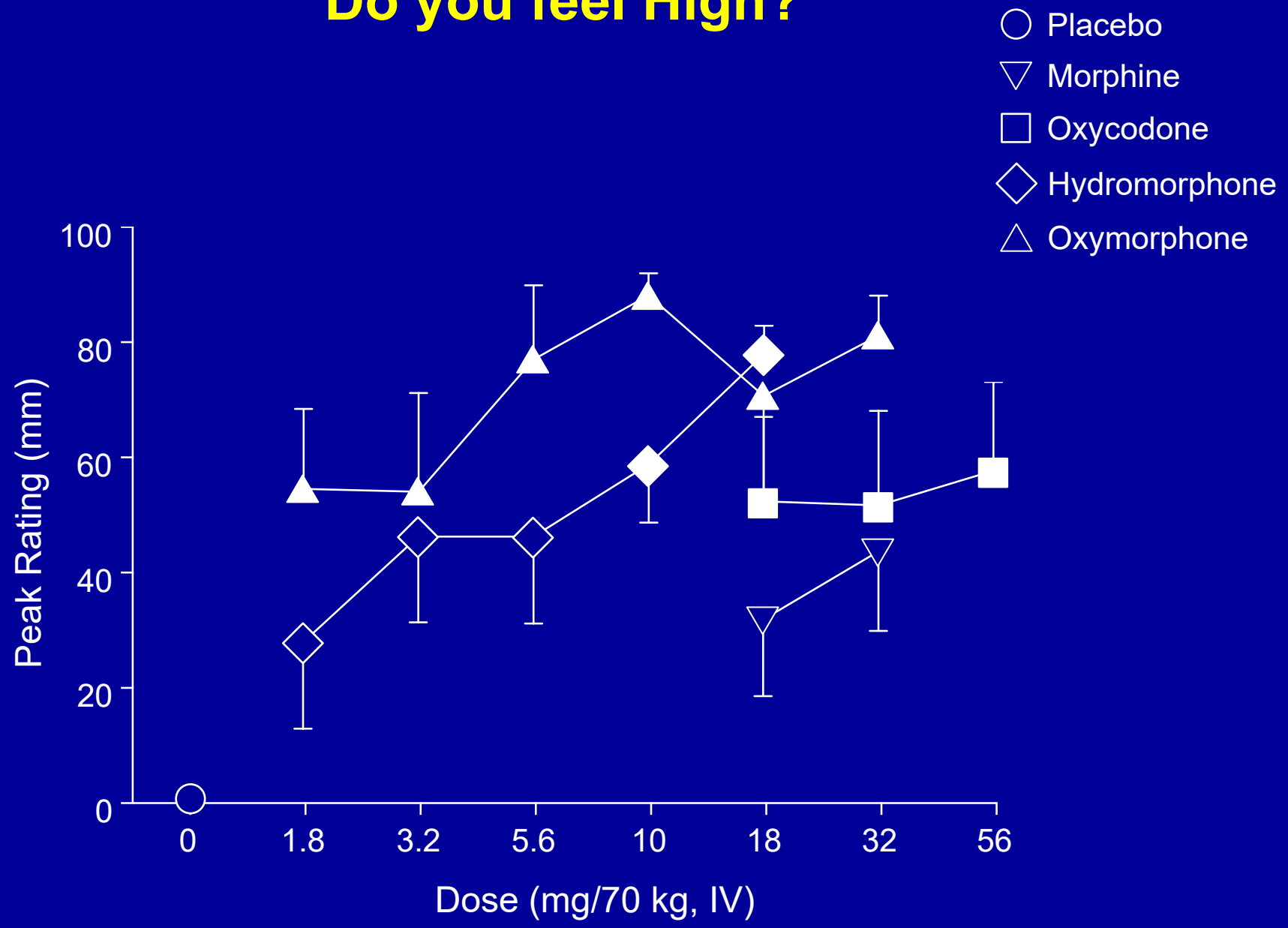

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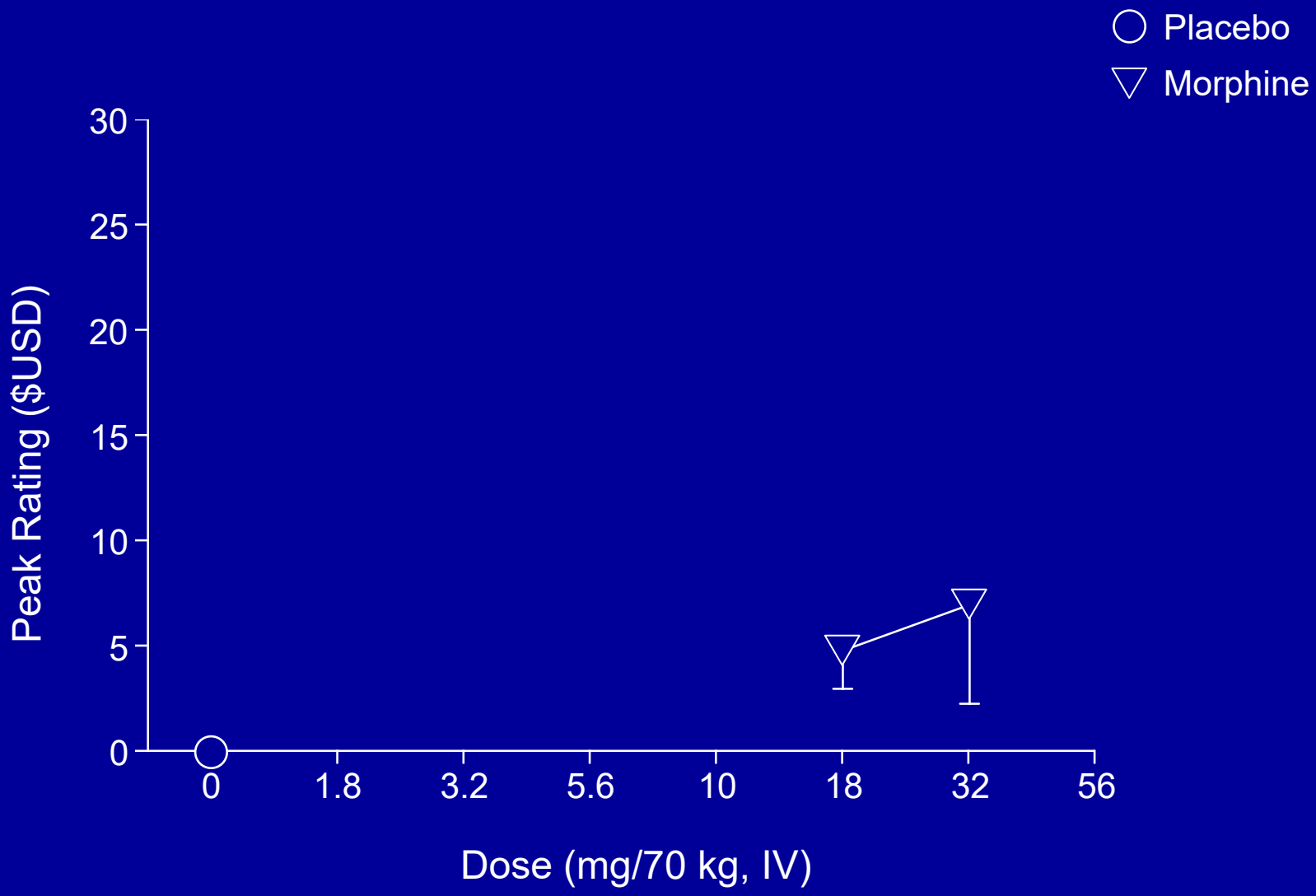

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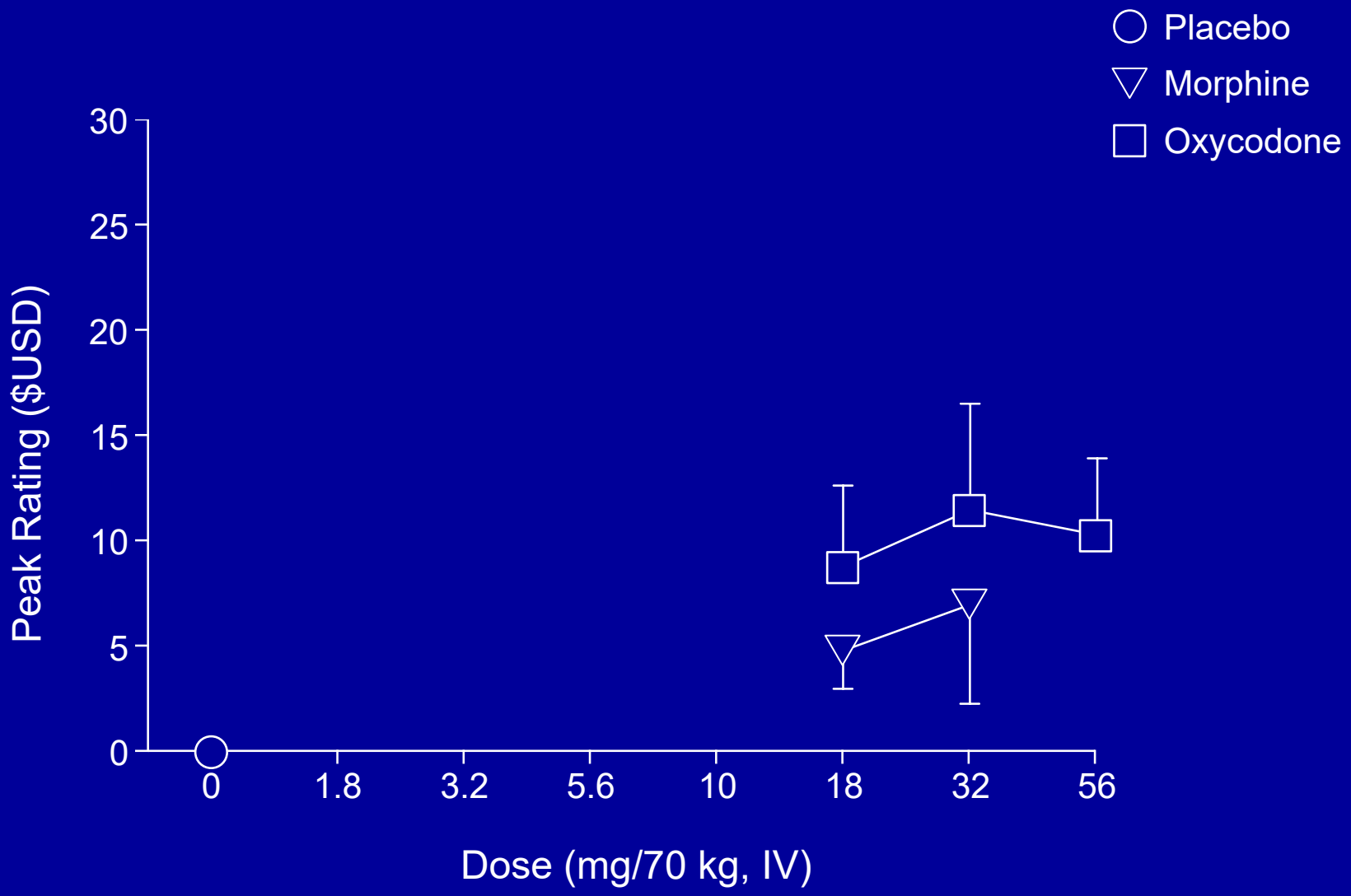

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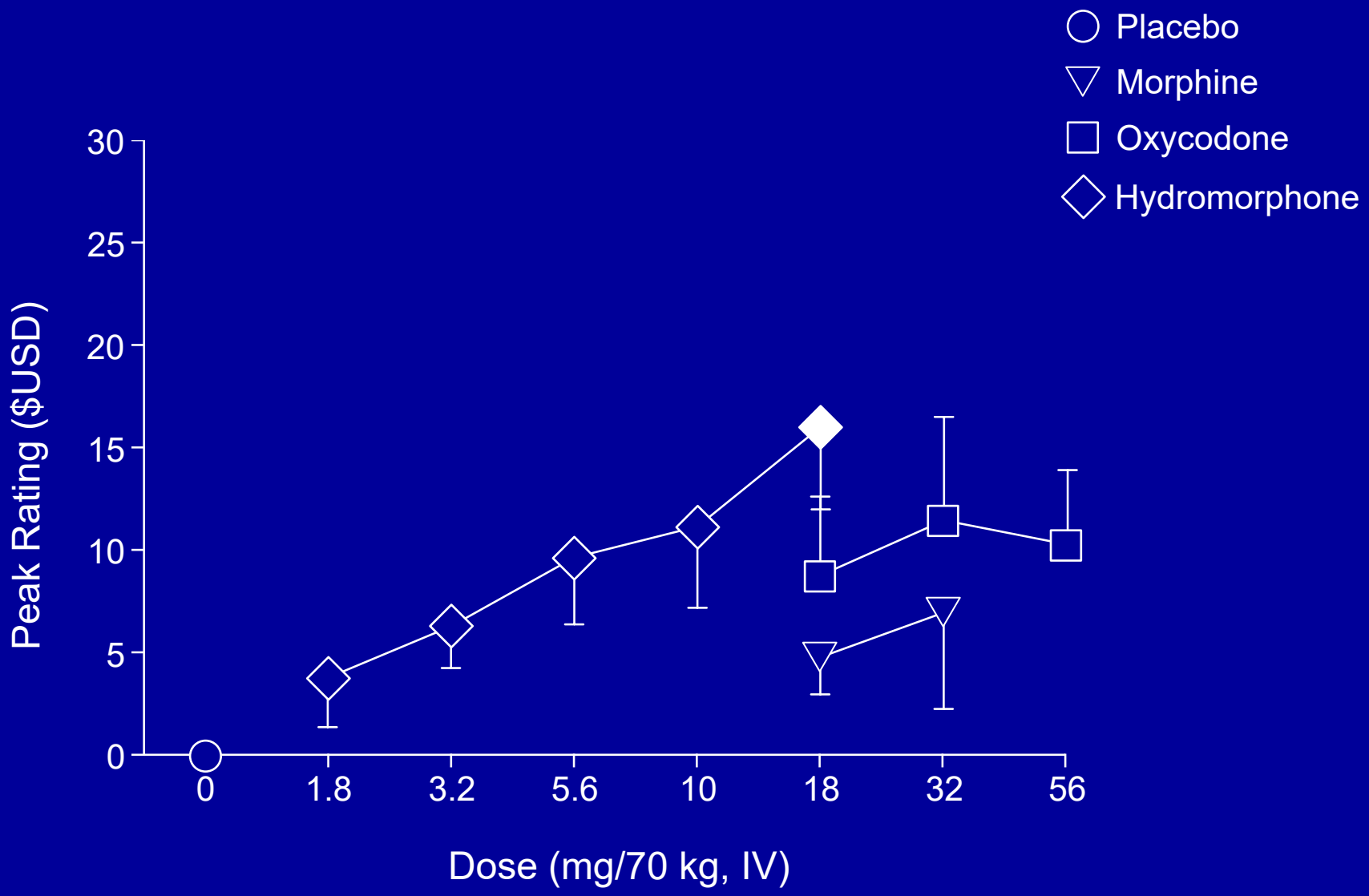

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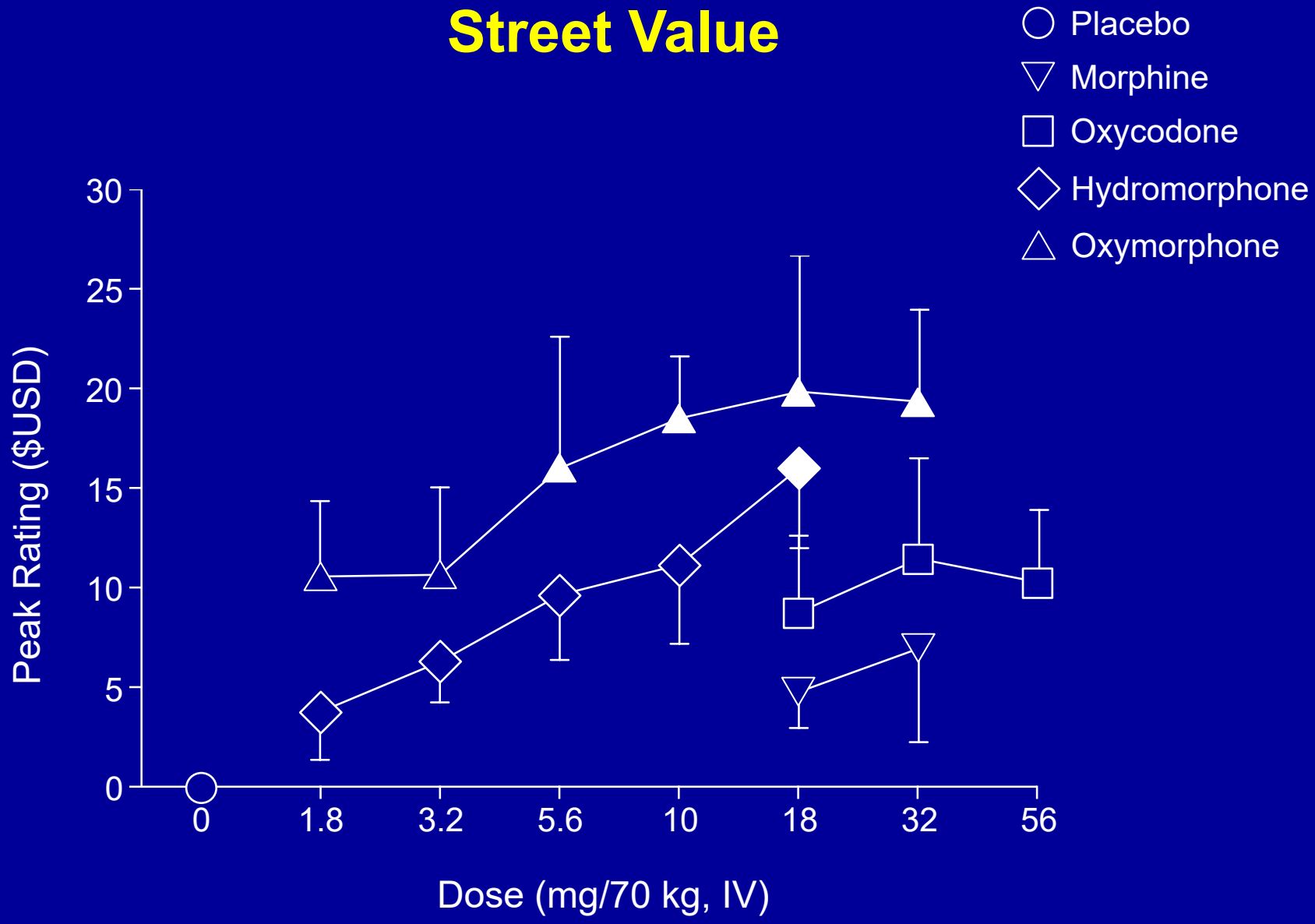

Relative Potency

Finney parallel lines bioassay was employed to assess oxymorphone relative potency

Two potency comparisons were conducted:

1) Oxymorphone and hydromorphone (3.2, 5.6, 10 mg)

2) Oxymorphone (1.8, 3.2, 5.6 mg) and oxycodone (18, 32, 56 mg)

Relative Potency

Oxymorphone vs. Hydromorphone

mg of IV oxymorphone ≈ 1 mg of IV hydromorphone

VAS Drug Liking	VAS Drug Effect	VAS High	Street Value	Pupil Diameter	$EtCO_2$
0.41	0.43	0.36	0.41	- -	0.82

Respiratory depression: oxymorphone 1.2-fold more potent ($EtCO_2$; $p<0.05$)

Abuse liability: oxymorphone was 2.3 – 2.8-fold more potent ($p<0.05$)

Relative Potency

Oxymorphone vs. Oxycodone

mg of IV oxymorphone ≈ 1 mg of IV oxycodone

VAS Drug Liking	VAS Drug Effect	VAS High	Street Value	Pupil Diameter	$EtCO_2$
0.07	0.08	- -	0.07	- -	- -

Abuse liability: oxymorphone was 12.5 – 14-fold more potent than oxycodone ($p<0.05$)

Summary

All of the drugs tested produced prototypical, dose-related opioid effects (e.g., miosis, increased $EtCO_2$)

Abuse potential of IV oxymorphone far exceeded the comparator opioids; moderate dose (5.6 mg/70 kg) produced peak effects ≥ all other comparator doses

Significant abuse-related effects of oxymorphone at comparatively low doses (1.8-5.6 mg/70 kg)

These data align with surveillance reports indicating that, after adjusting for prescription rates/availability, oxymorphone was injected at the highest rates, relative to other prescription opioids (7x higher than other rx opioids)

Conclusions

These high rates of injection are likely due to:

1) low oral bioavailability of oxymorphone, increasing misuse by routes with greater bioavailability
2) easy manipulation of oral product to access high doses (40 mg)
3) pharmacological action of oxymorphone (high degree of binding affinity, intrinsic activity)
4) rapid transport across the blood-brain barrier
5) high relative potency, particularly on abuse potential outcomes

Overall, oxymorphone may pose a disproportionately high degree of risk and public health harm relative to other full agonist IV prescription opioids

Acknowledgements

UK Research Team

Sharon L. Walsh, PhD
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Funding

National Institute on Drug Abuse
R01DA016718 (SLW)

U.S. Food and Drug Administration
HHSF223201710120C (SLW)
HHSF223201710119C (SDC)

National Center for Advancing of Translational Sciences
UL1TR001998 (UK CTSA)