

# **Post Operative Bunionectomy Pain and Analgesic Drugs: Model and Effect Size Characteristics of Standard Oral Analgesics**

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# ABSTRACT # 2711

- **Aim of Investigation:** To describe the effect size (assay sensitivity) produced by several prototypical analgesics in the bunionectomy acute pain model.
- **Methods:** A number of double blind, randomized, parallel design studies have been conducted in patients undergoing a first metatarsal bunionectomy (with osteotomy) under regional anesthesia and propofol sedation have been conducted. Study designs are similar, with dosing either immediately following surgery or on the morning of the next day, when patients experienced moderate to severe pain (VAS  $\geq 40$  mm). Using the bunionectomy model, this poster will summarize the effects size of commonly used oral standards of comparison (ibuprofen 400 mg, morphine 60 mg, rofecoxib 50 mg and naproxen 550 mg). While a variety of time-points have been used in these studies for consistency purposes, only data on Pain intensity and Pain Relief measured up to 8 hrs. and derived variables will be shown.
- **Results:** This poster will summarize the effect sizes (Cohen's D) between active drug and placebo in the various trials that utilized the Bunionectomy Model. These ranged from 0.35 to 0.76 for NSAIDs and from 0.66 to 1.48 among opioid containing analgesics. The following treatments have all separated from placebo in different studies: rofecoxib 50 mg, naproxen 550 mg, ibuprofen 400 mg, morphine 60 mg and acetaminophen / oxycodone 1000/10 mg.
- **Conclusions:** The Bunionectomy model appears to provide a robust and practical model with excellent assay sensitivity. Patients medicate for at least 5 days postoperatively and this appears to provide a useful single dose, multi-day and/or multiple dose model for evaluation of new analgesics. Most drugs used as standards of comparison readily separated from placebo for measures of efficacy (NSAIDs, Cox-II inhibitors and opioids). This model also lends itself to studies in multiple settings such as ambulatory surgical centers and outpatient hospitals. We hypothesize that the bunionectomy acute pain model responds similarly to major orthopedic surgery in which patients experience severe and prolonged (5-10 days) postoperative pain.
- **Acknowledgments:** All authors are employees of SCIREX Corporation. No financial support from any sponsor was received to support this preliminary analysis.

# What is a Bunion?

## *(Hallux Abducto Valgus)*

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A bunion is excess or misaligned bone in the joint.



*“Acquired deformity caused by abnormal mechanics at the first metatarsophalangeal joint” (Root, Orien & Weed, 1977)*

# Etiology and Presenting Signs and Symptoms

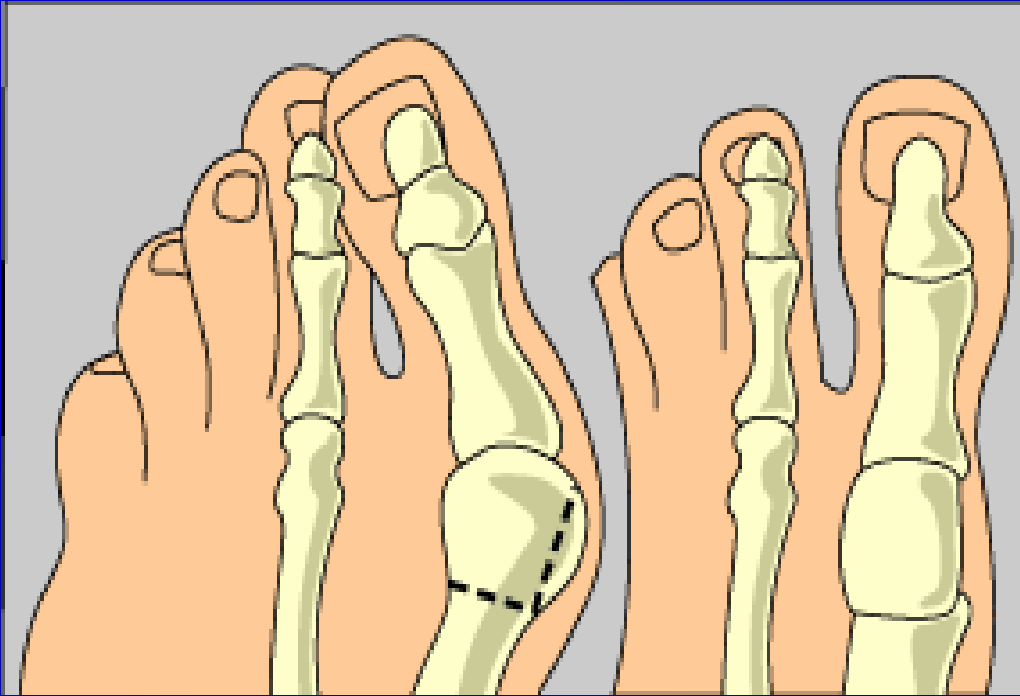
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- **Heredity**
  - Abnormal foot mechanics
  - \*Approximately 33% of adults have some degree of hallux valgus deformity
- **Complicated by degenerative bone or joint disease such as arthritis**
- **Accelerated by high heels which force toes together and displace weight onto the forefoot**
- **Pain under plantar head (sesamoid pain)**
  - numbness/burning
  - Functional limitations
  - limited range of motion
- **Joint deformity with associated deformity of the toes**
  - specialty shoes

# WHAT IS A BUNIONECTOMY?

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A “typical” bunionectomy involves excision of the medial aspect of the first metatarsal with osteotomy and internal fixation of the first metatarsal



## Basic Bunionectomy Procedure

- Skin incision
- Capsulotomy
- Osteotomy of the head of the first metatarsal
- Fixation of proximal bone segments
- Closure

# INTRODUCTION

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Bunions are deformities of the foot manifested by pathologic bone depositions, joint deformity and pain on standing or walking. Bunions are commonly treated conservatively (orthotics, wider shoes) until they become functionally or cosmetically unmanageable to the patient. Surgical management is an option of choice to improve function, decrease pain and correct deformity of the foot. Post-operative pain is a frequent and predictable sequela of this surgery and it must be managed in outpatient hospital or ambulatory care settings as well as when the patient returns to his/her home.

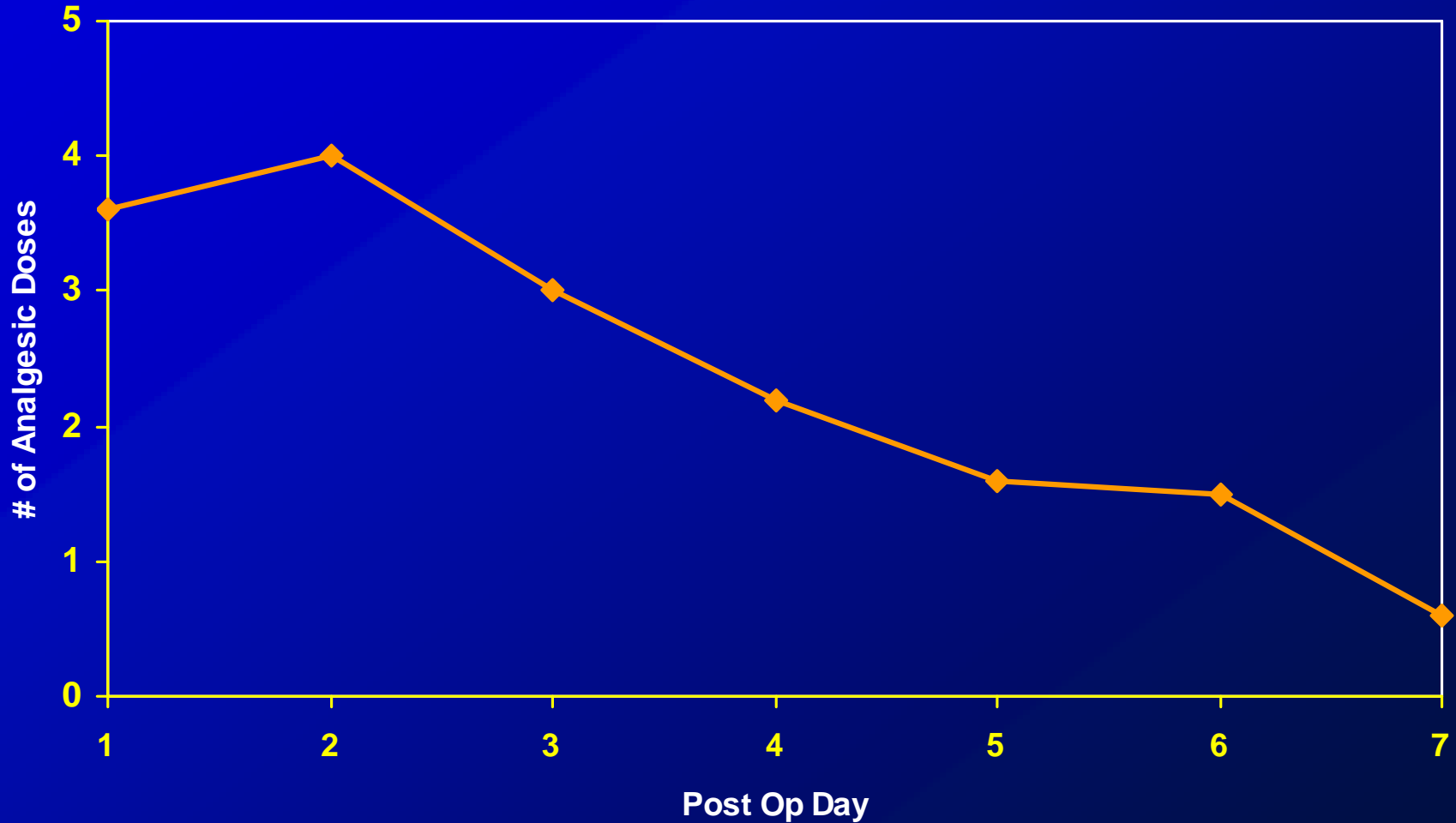
Data presented at the IASP meeting in 2002 provided preliminary support for the feasibility and development of a new post-operative, orthopedic pain model based on bunionectomy surgical procedures. Further refinements of the model over the past three years, have resulted in a practical and predictable post-operative model in which various analgesic interventions can be assessed. We have conducted a number of pilot and full RCTs of both NSAIDs (COX II & non-selective) and opioids (single entity & combination) using: pre-treatment, post-operative single dose and post-operative multiple dose designs. The Bunionectomy model has demonstrated assay sensitivity in both NSAID and opioid classes. In addition, our work has indicated that the model demonstrates characteristics that are desirable for a robust acute post-operative pain model:

- **Elective surgery and predictable post-op course**
- **Ability to standardize the pre-op and anesthetic regimens**
- **Ability to standardize the surgical procedures**
- **Use of both in-patient and out-patient settings**
- **High reliability of patient compliance (both dosing & pain assessments)**
- **Uses trained analgesic research nurses and staff**
- **Readily available target population**
- **Potential for single, multiple day and multi-dose trials**
- **Decreased RCT cycle time (FPI-LPO) relative to other orthopedic models**

The purpose of this poster is to: 1. present selected data from recent trials demonstrating the assay sensitivity/effect size of various compounds in the Outpatient Orthopedic Pain Model and; 2. begin to assess the “effect size” of the model in comparison to other contemporary post-operative pain models.

# Figure 1.

## Typical Post-Bunionectomy Analgesic Requirements (Number of Analgesic Drug Doses/Day)



# “Prototypical” Study Design

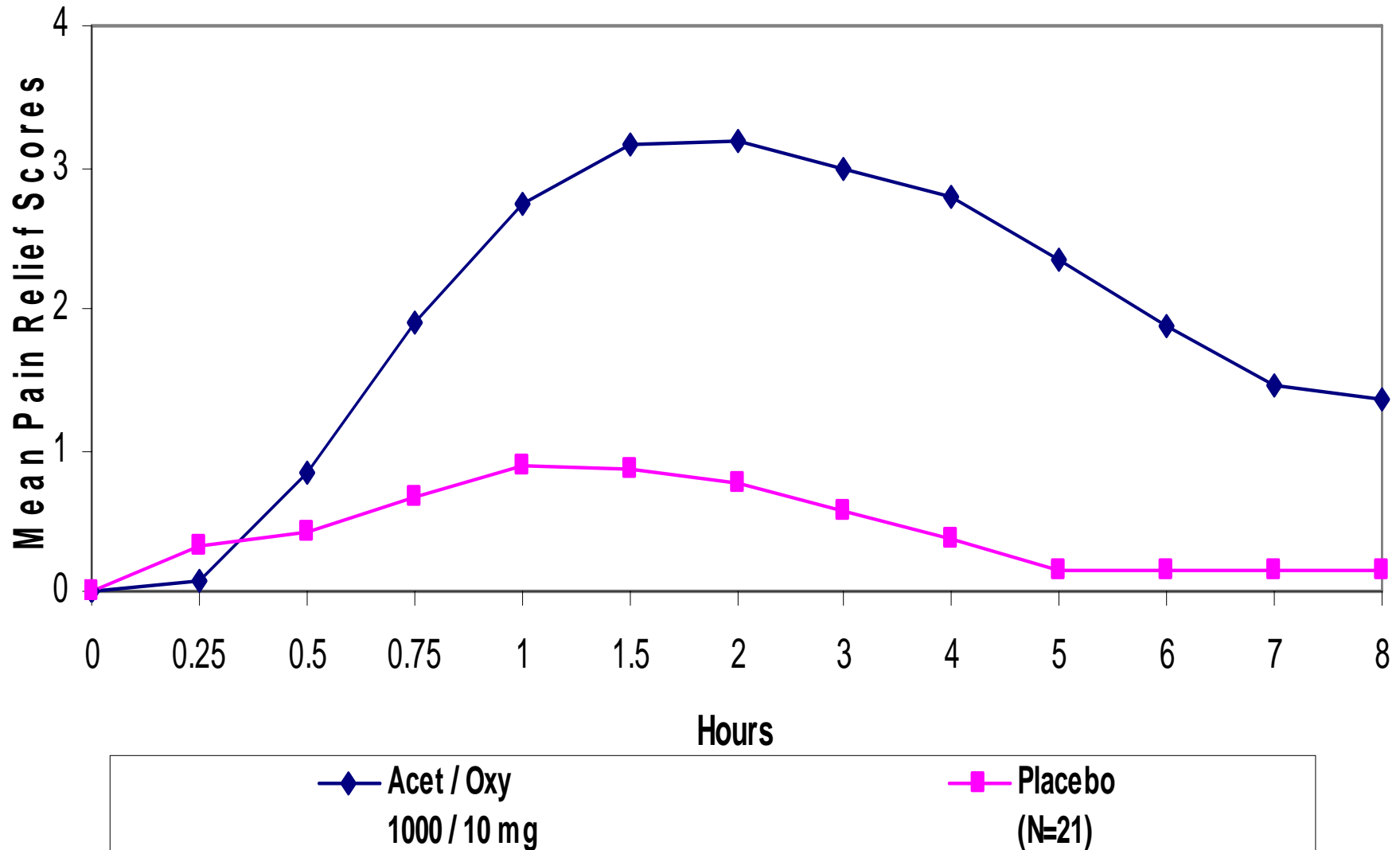
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- Randomized; double-blind; single oral doses
- Standardized surgical procedure
- Standardized anesthetic regimen
- Standardized analgesia on day of surgery
  - Regional anesthesia and propofol sedation
  - PRN oral analgesics
- At least 4 hour washout of all analgesics
- Dosed on surgery day or post-op day 1 when pain was “moderate” or “severe” and VAS  $\geq 40$  mm/100 mm
- Serial pain intensity and pain relief assessments and globals over 1 to 5 days
- Effect Size calculation:  $(M_{\text{comparator}} - M_{\text{placebo}}) / \text{Pooled S.D.}$

# Figure 2a.

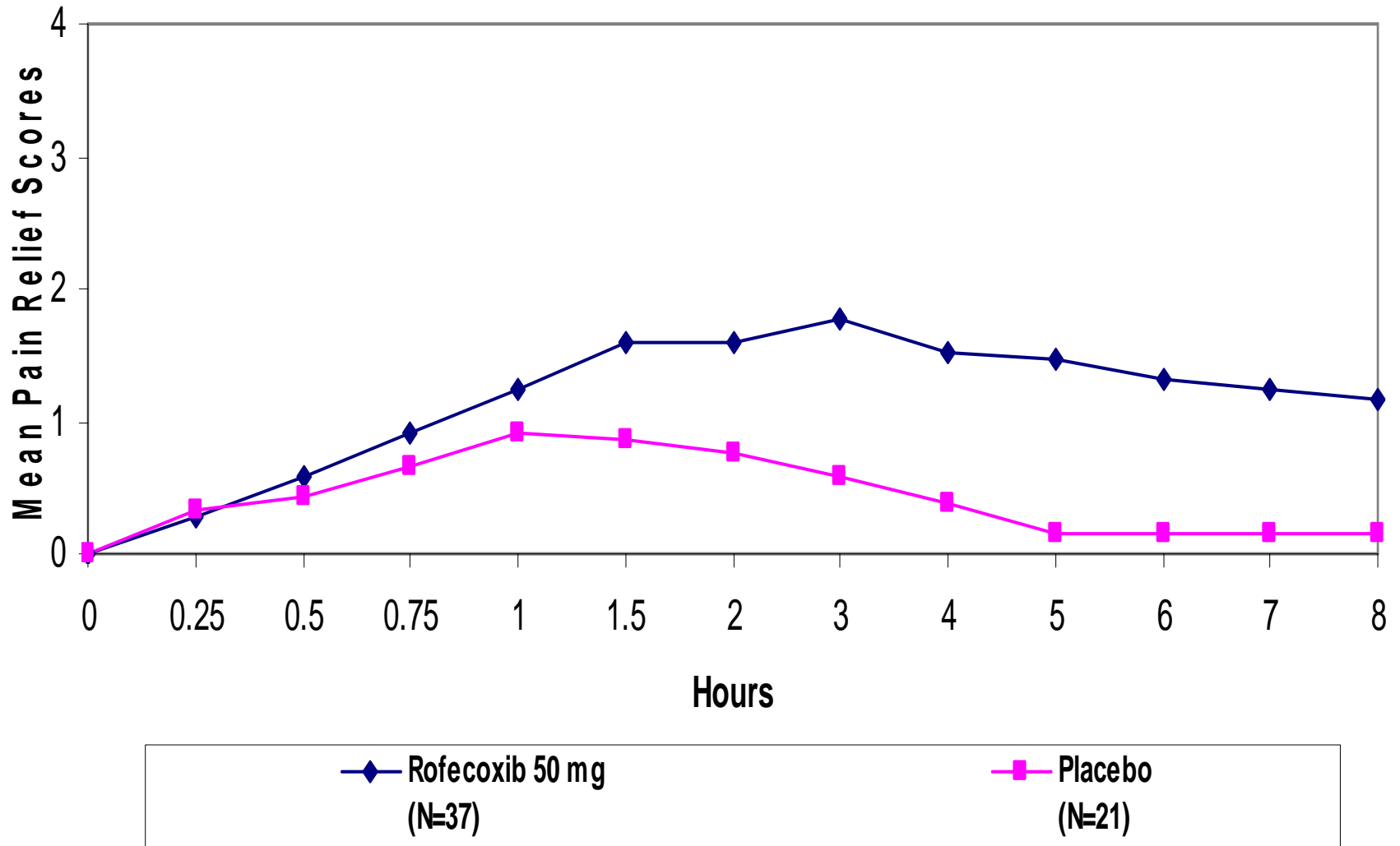
## Bunionectomy

Pain Relief Time-Effect Curve (TOTPAR 8;  $p < .05$ )



# Figure 2b. Bunionectomy

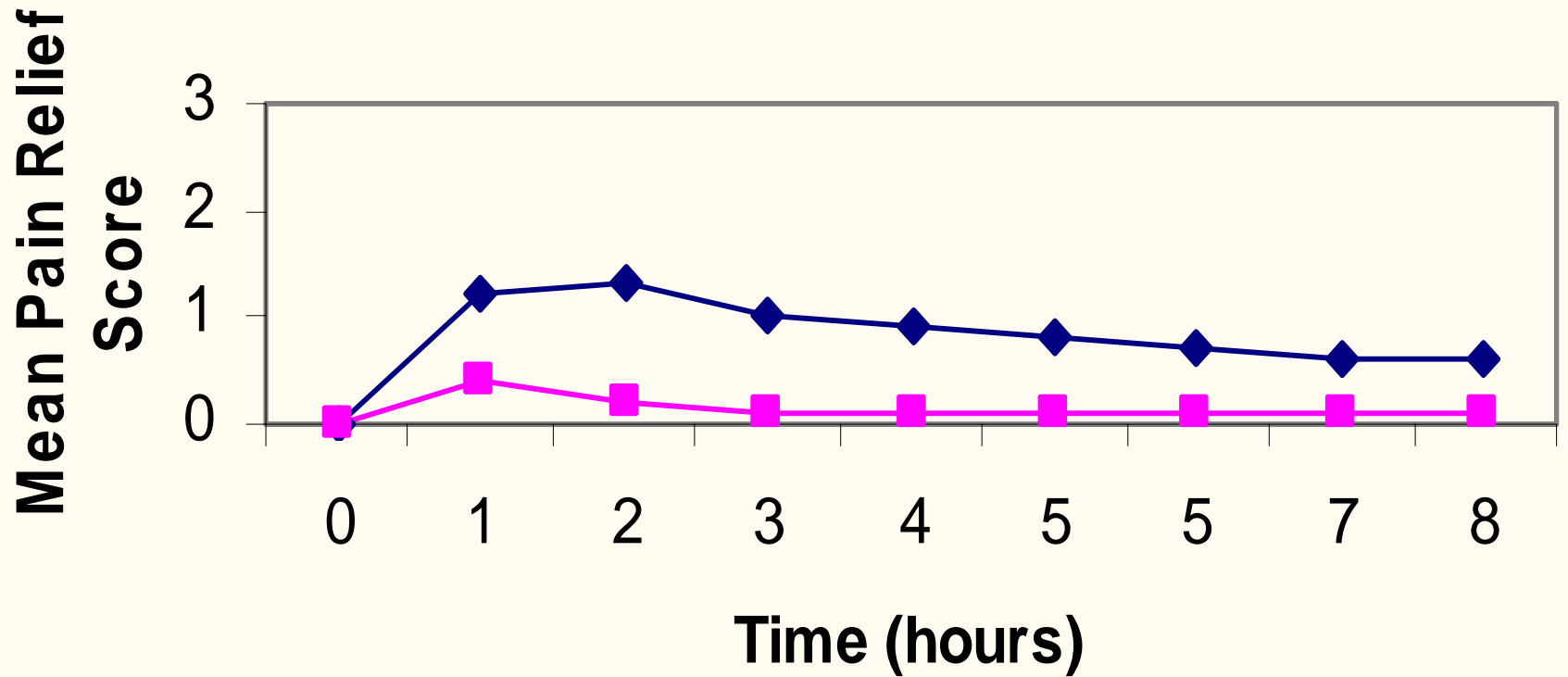
Pain Relief Time-Effect Curve (TOTPAR 8 ;  $p < .05$ )



# Figure 3a.

## BUNIONECTOMY

Pain Relief Time-Effect Curve (TOTPAR 8;  $p < .05$ )

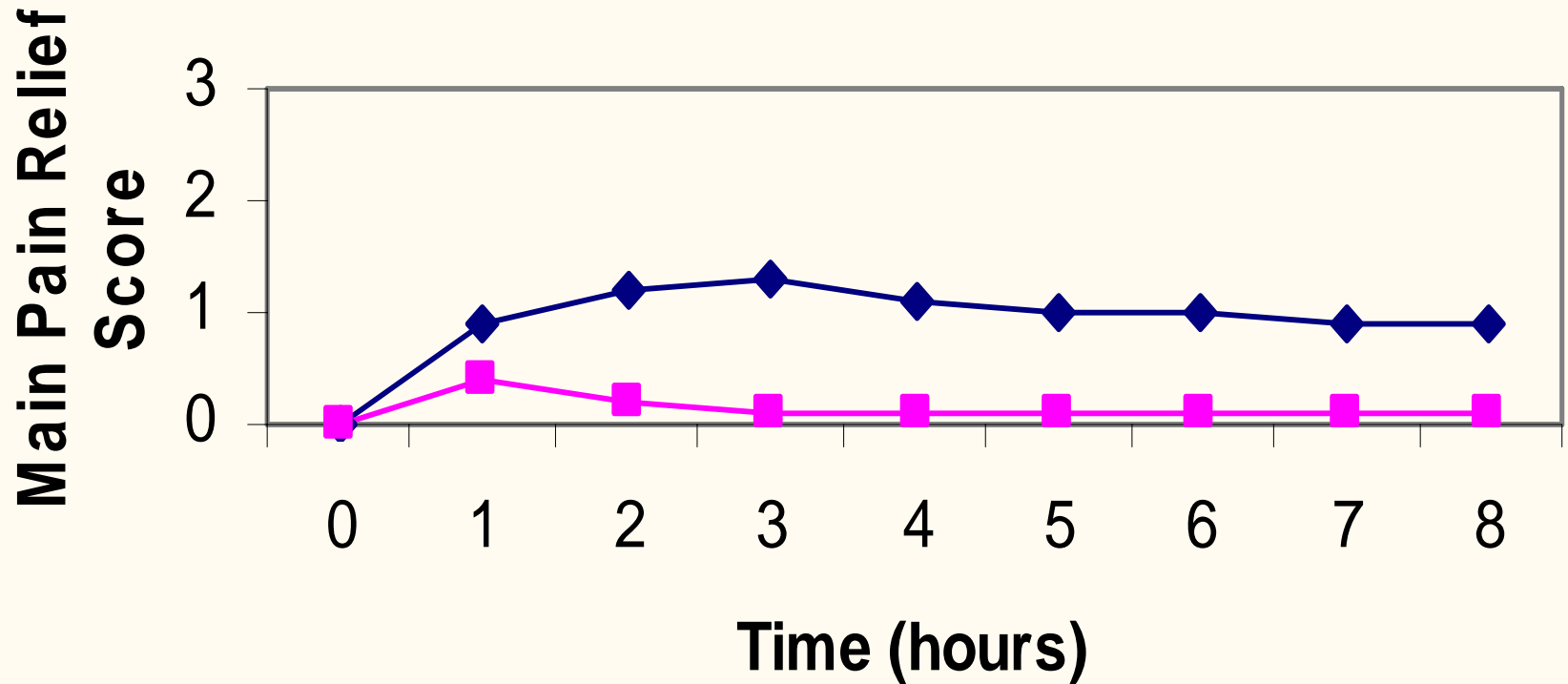


—◆— Morphine 60 mg. (n=63) —■— Placebo (n=65)

# Figure 3b.

## BUNIONECTOMY

Pain Relief Time-Effect Curve (TOTPAR 8;  $p < .05$ )

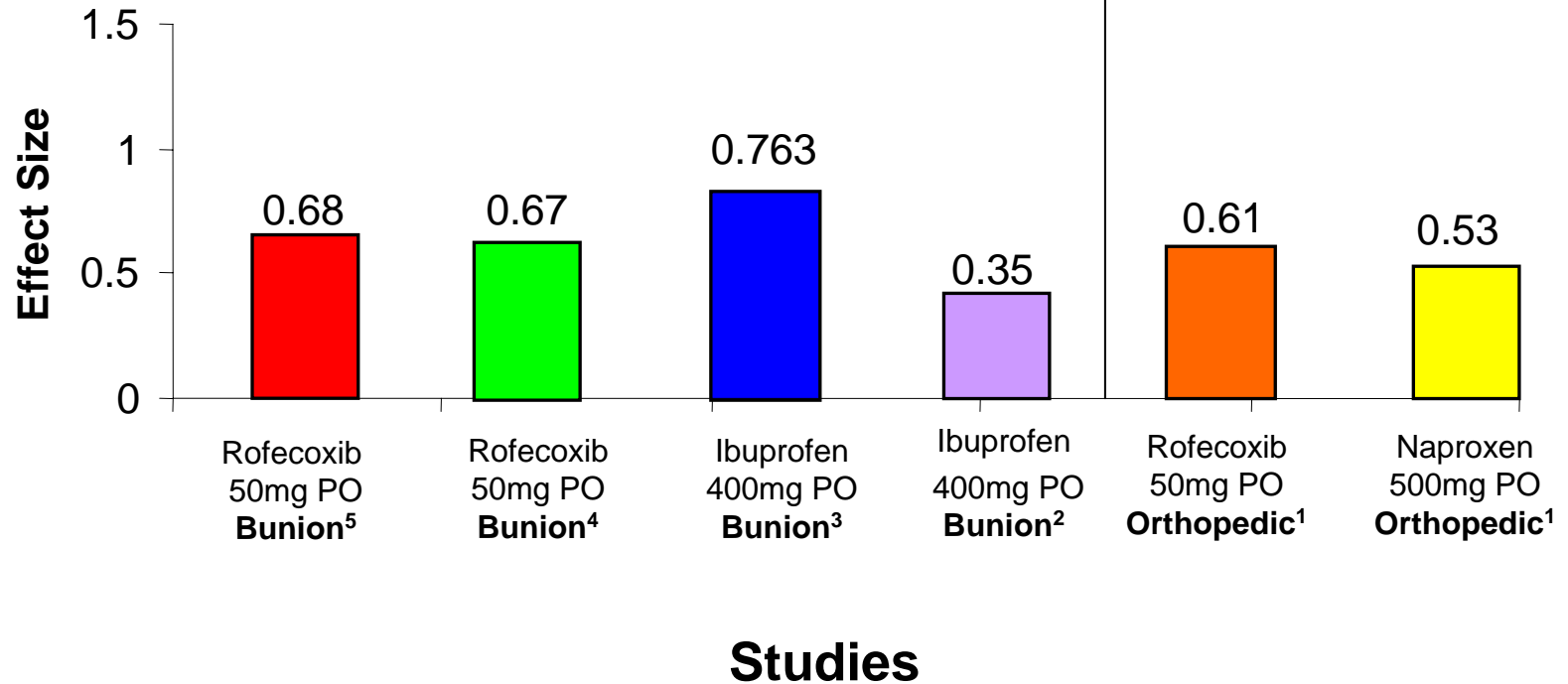


—◆— Ibuprofen 400mg (n=64) —■— Placebo (n=65)

# Figure 4b.

## NSAID/COX II Effect Size

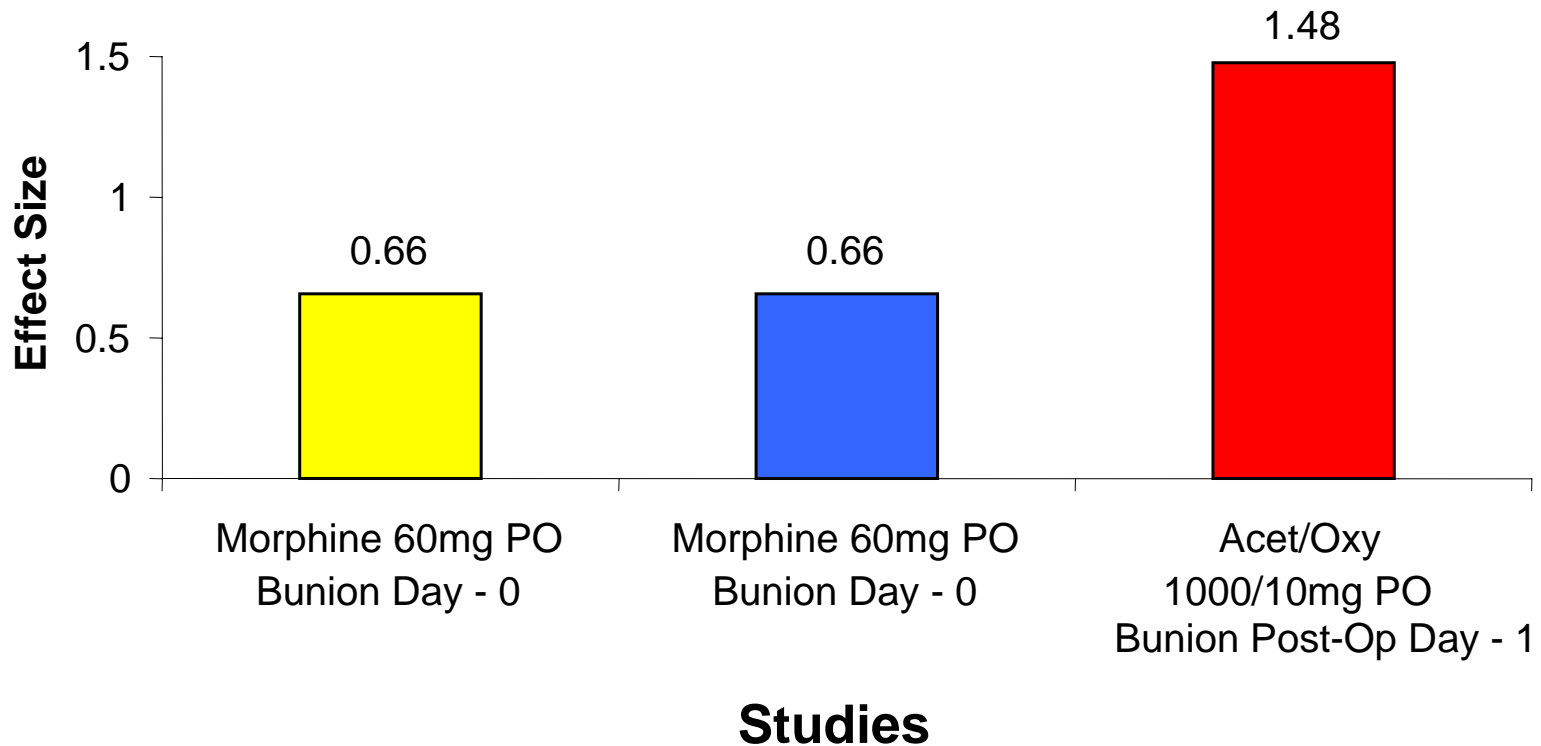
(Based on SPID-8, comparator-active vs. placebo - all p's < .05)



# Figure 4a.

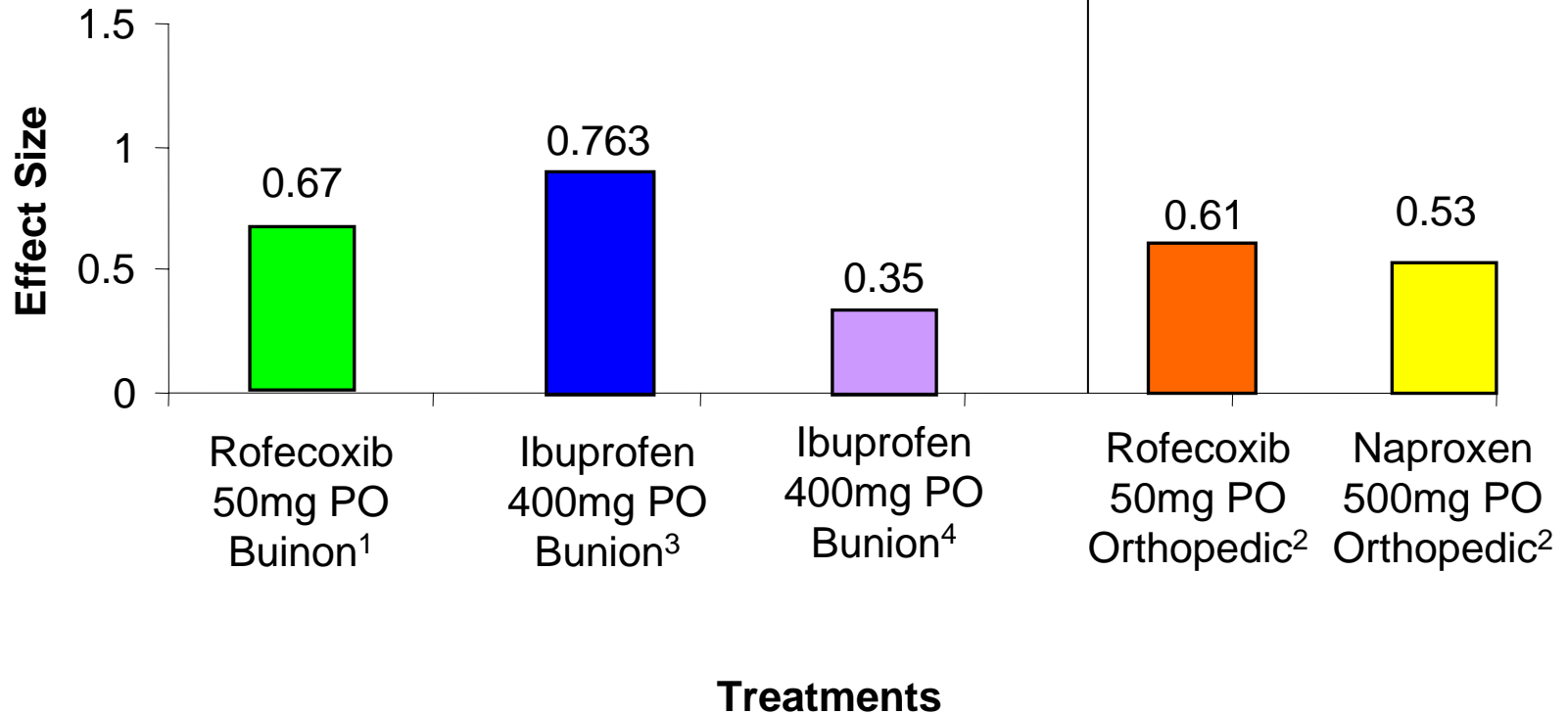
## Opioid Effect Size

(Based on SPID-8, comparator/active vs. placebo - all p's<.05)



# Figure 4b. NSAID/COX II Effect Size

(Based on SPID-8, comparator/active vs. placebo - all p's<.05)



# Discussion/Conclusions

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- We conclude that the bunionectomy model has good validity (assay sensitivity) and reliability relative to other pain models.
- Post-bunionectomy pain appears to be a robust and versatile pain model to assess Cox II inhibitors, single entity opioids and combination analgesics.
- The model allows for a variety of dosing regimens
- This model lends itself to studies in multiple settings such as ambulatory surgical centers and outpatient hospitals.
- Data indicate that the bunionectomy pain model responds similarly to major orthopedic surgery in which patients experience severe and prolonged (5-10 days) post-operative pain.
- Experience thus far with the model shows markedly decreased cycle recruitment time compared too “classic” orthopedic models.