

IMPACT-XI

Research Design Considerations for
Clinical Trials of Perioperative
Analgesic Medications
to
Optimize Acute Postoperative Pain
Management and Recovery

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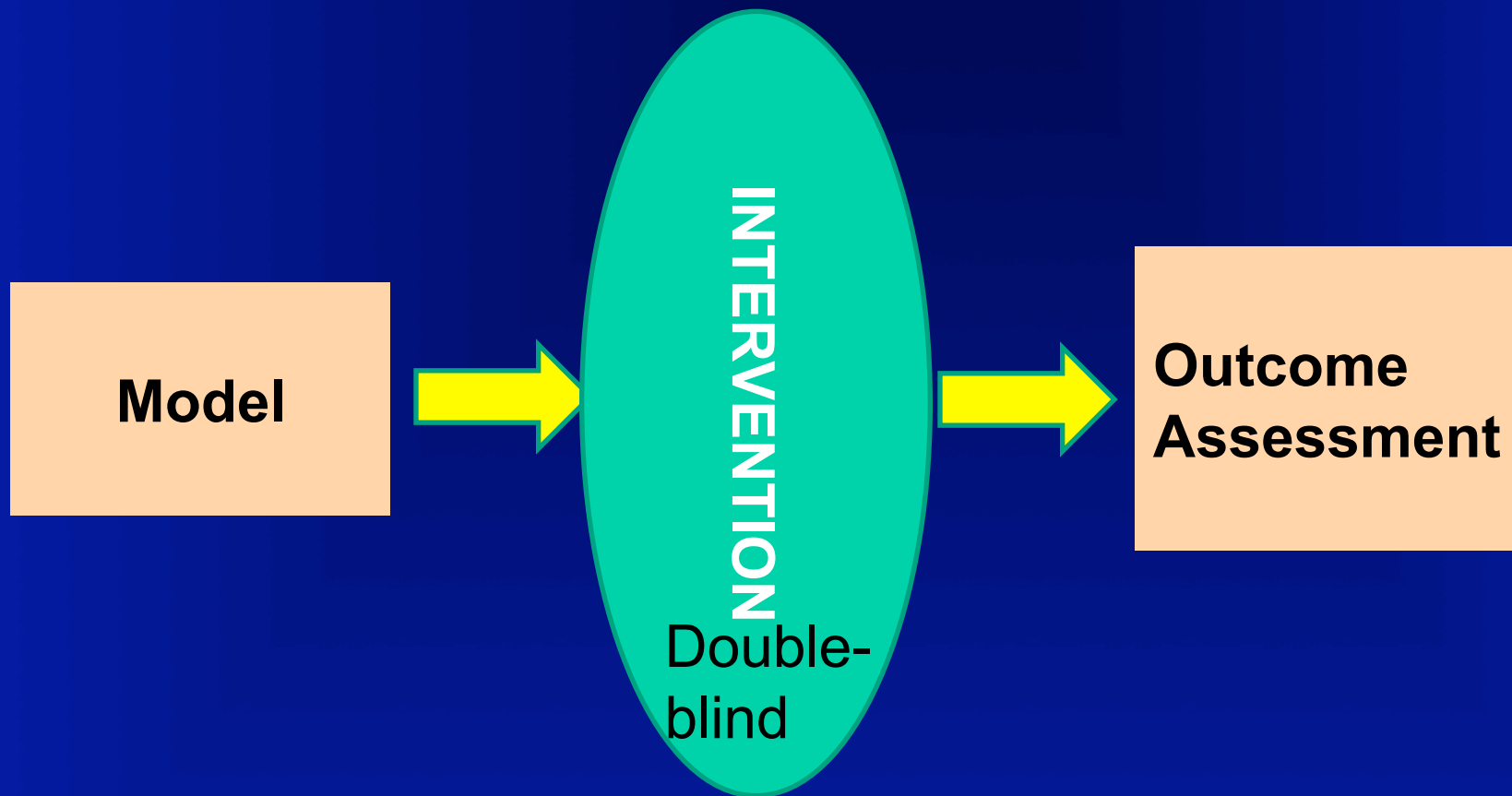
**Optimal Study Design will depend on
the Aim of the Study and
the Investigators' Interests**



Varying Goals for a Study

- Efficacy of a new drug in perioperative pain management: *Clinical researcher/ Industry*
- Prevention of persistent pain after surgery: *Clinical researcher/ Industry*
- Best method for fast tracking a patient: *Hospital administrator/ Insurer-Payer*
- Best study methodology to show efficacy and safety of a drug: *FDA/ Industry*
- Mechanisms, site of action: *Basic scientist*

Basic Study Design



*Jenah-America's Next Top Model before and after
Courtesy: Meera R- pier59 studios, NY*

Selecting the Optimal Model

- Mixed surgical models
 - Variability in injury, pre- and postop pain?
- Surgery specific- Generalizability?
 - Inpatient vs outpatient surgery
 - Visceral vs Somatic pain
- Select Population- ASA 1, 2
 - Problems specific to a population: e.g., Age, comorbidity (hepatic, renal, cardiac)
 - Variability in Pain: e.g., sex, ethnicity

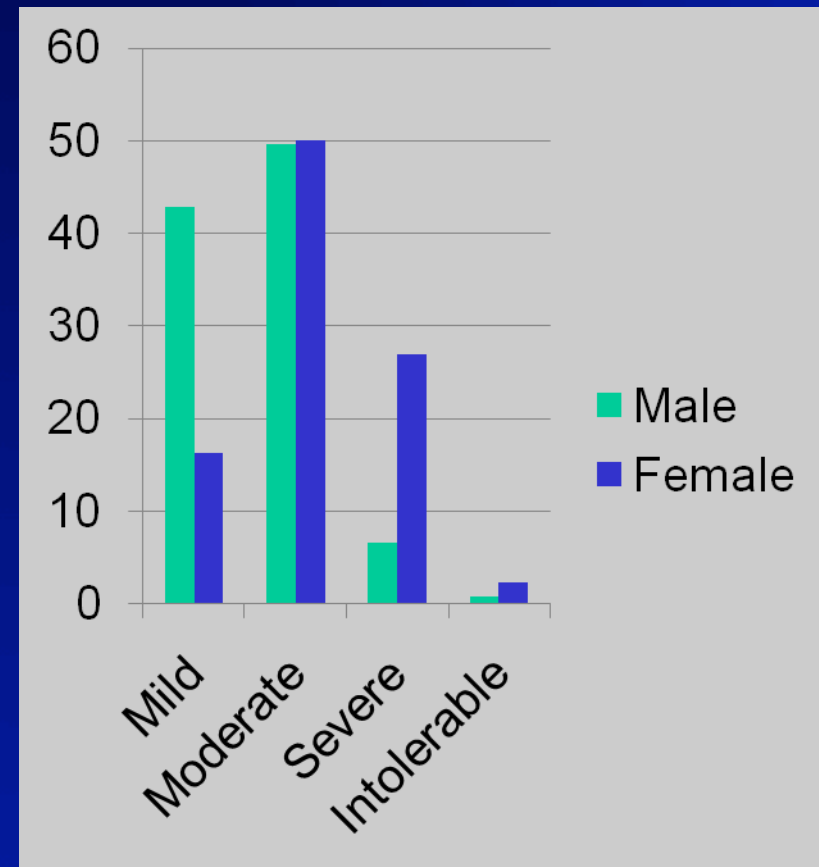
Procedure-specific Postoperative pain treatment recommendations



- **Postulate:** different types of surgical procedures have their unique pain characteristics and clinical consequences
- Procedure specific evidence-based recommendations
- A clinical tool for postoperative pain management in common surgical procedures

'Gender is a confounding factor in pain trials' - arthroscopic surgery

- Women reported an 84% incidence of at least moderate postoperative pain
- Men reported 57% moderate or higher pain ($P < 0.001$)



The Model

Studies with Intra-articular morphine

- Analgesic effect of intraarticular morphine after arthroscopic knee surgery. *C Stein, K Comisel, E Haimerl, A Yassouridis, K Lehrberger, A Herz, and K Peter*
- Comparison of postoperative analgesic effects of intraarticular bupivacaine and morphine following arthroscopic knee surgery. *Raja, S, Dickstein, R, Johnson, C*



The NEW ENGLAND
JOURNAL of MEDICINE

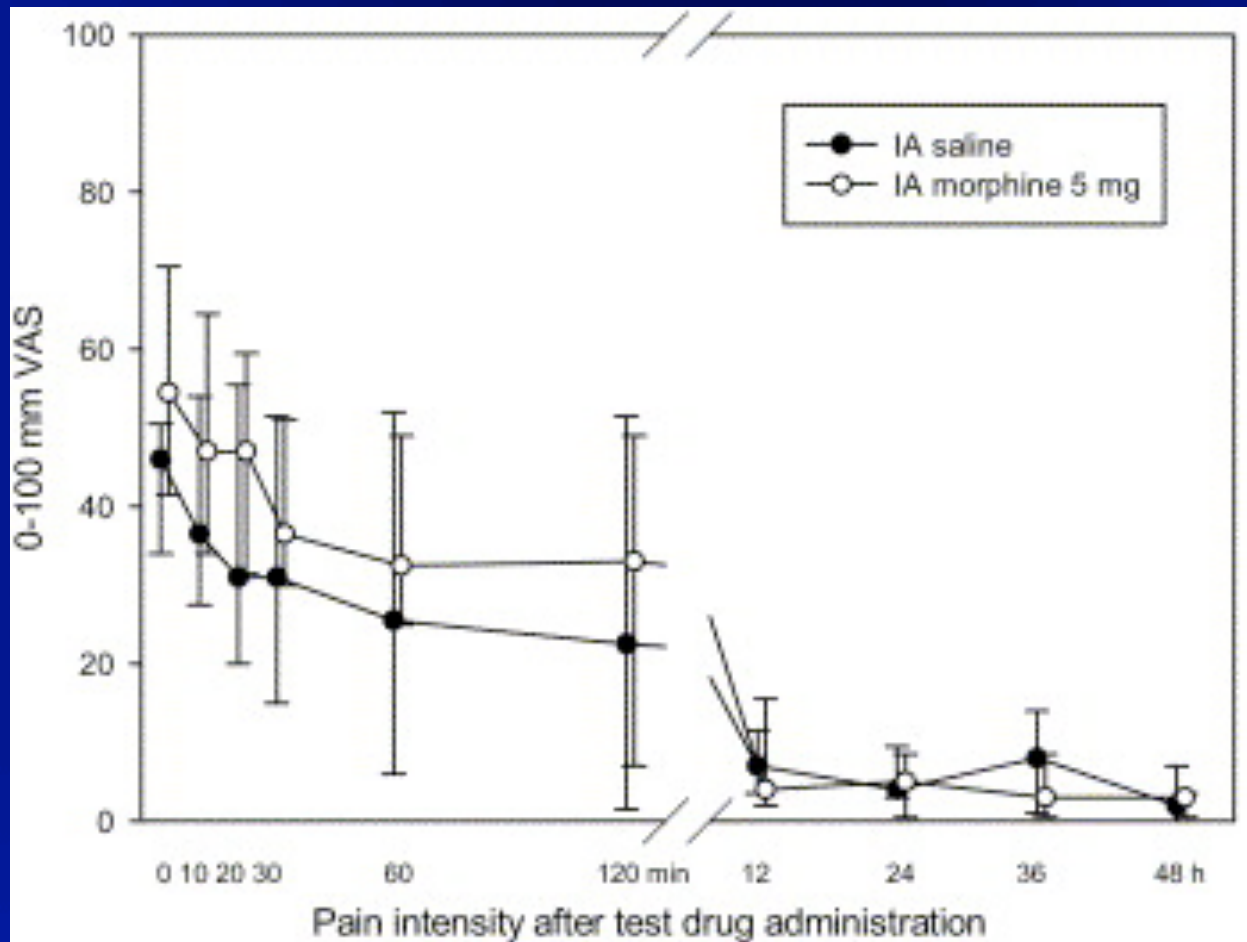
325:1123-1126, 1991



Anesthesiology
The Journal of the American Society of Anesthesiologists, Inc.

77:1143-1147, 1992

Intra-articular morphine does not produce significant pain relief in patients with moderate to severe pain

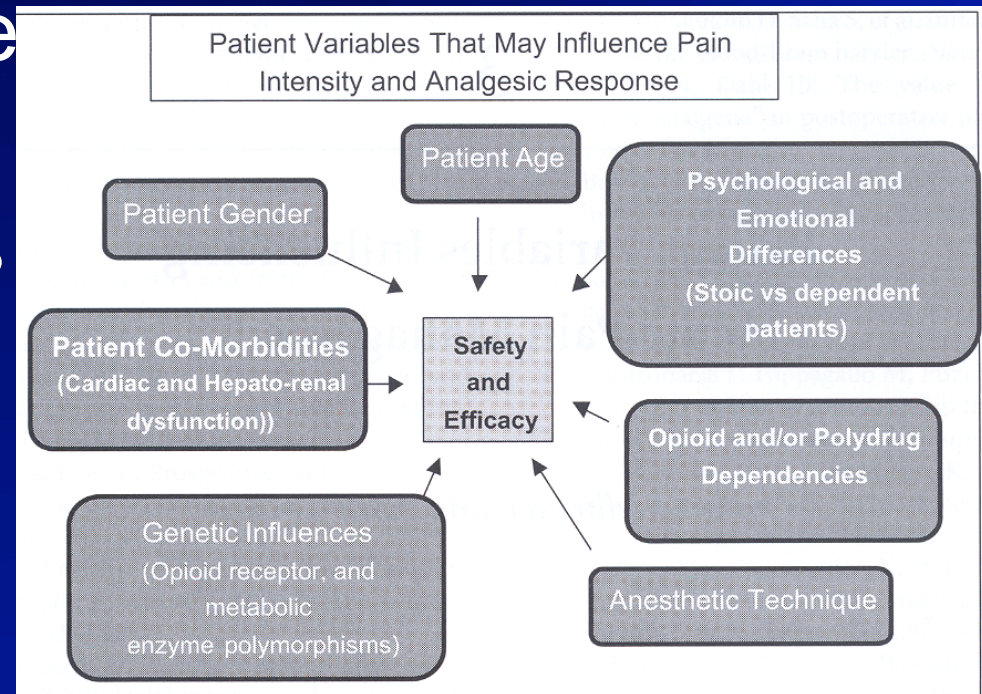


Solheim N et al.

Reg Anesth Pain Med. 2006 31:506-13

The Surgical Model- Summary

- Choice of procedure
 - Site, extent, surgeon
- Broad population vs select subgroup
- Match sex and age
- Caution: anesthetic used



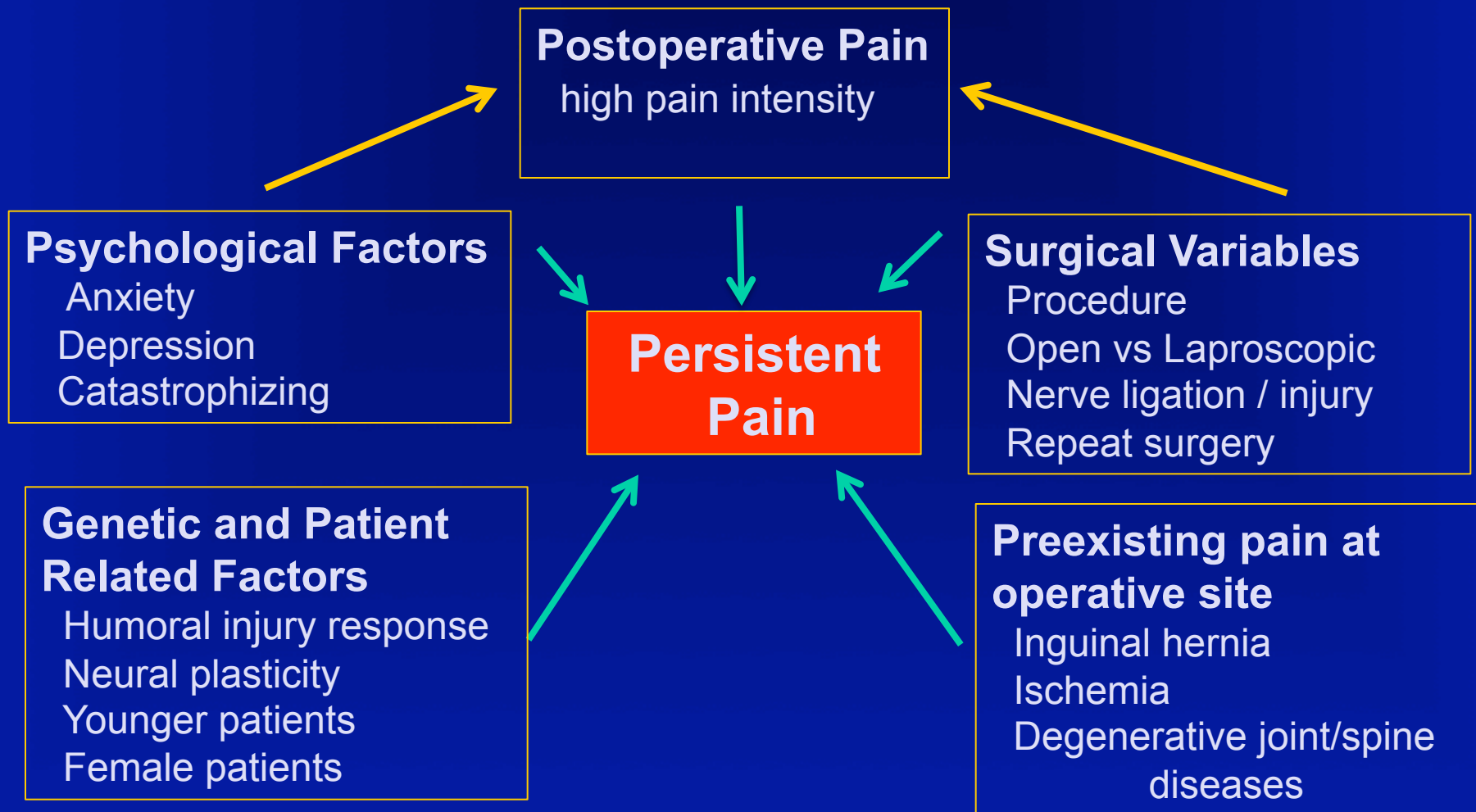
Optimizing Postoperative Pain and Recovery: Study Design

Identifying the problem
Surgical population

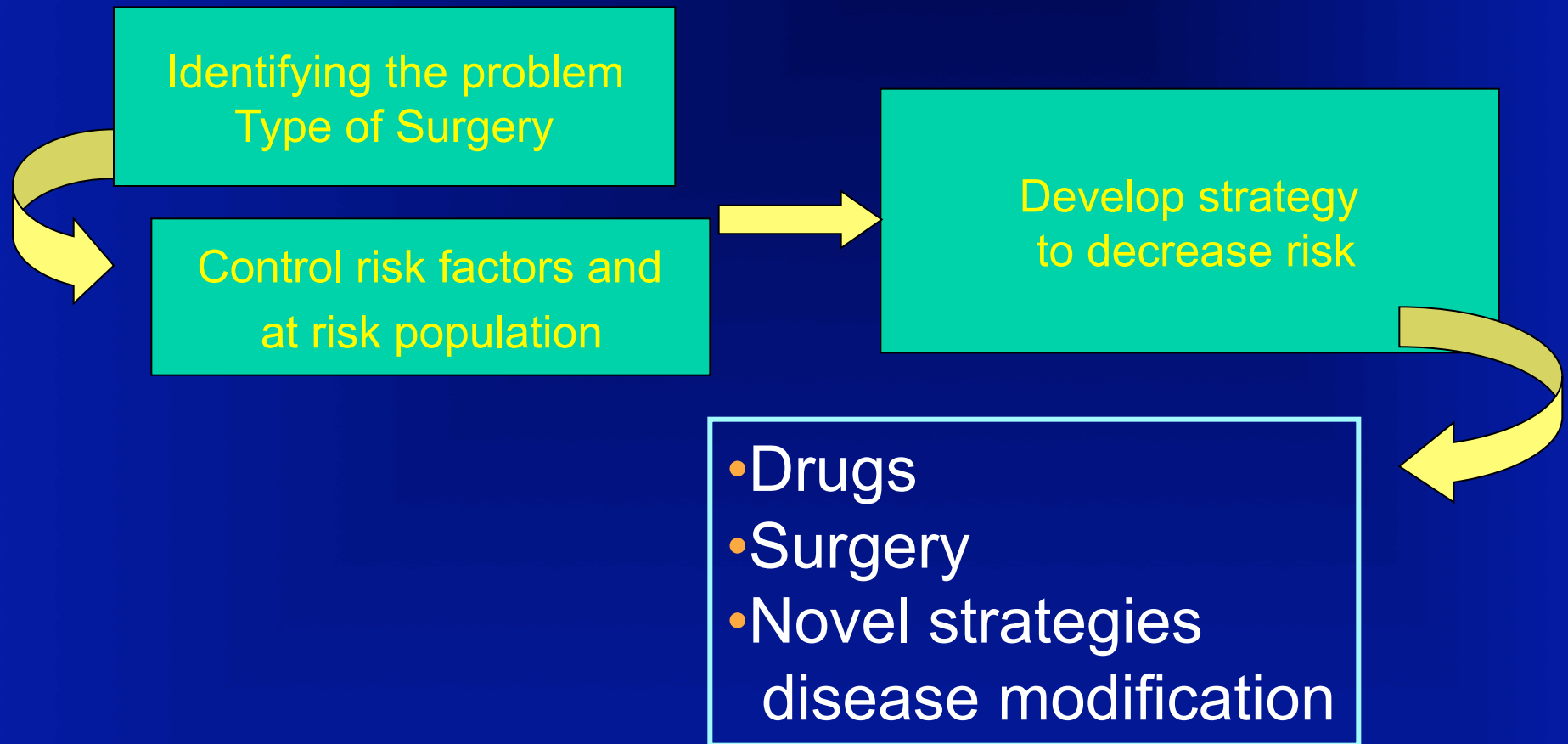
Control for risk factors and
at risk population



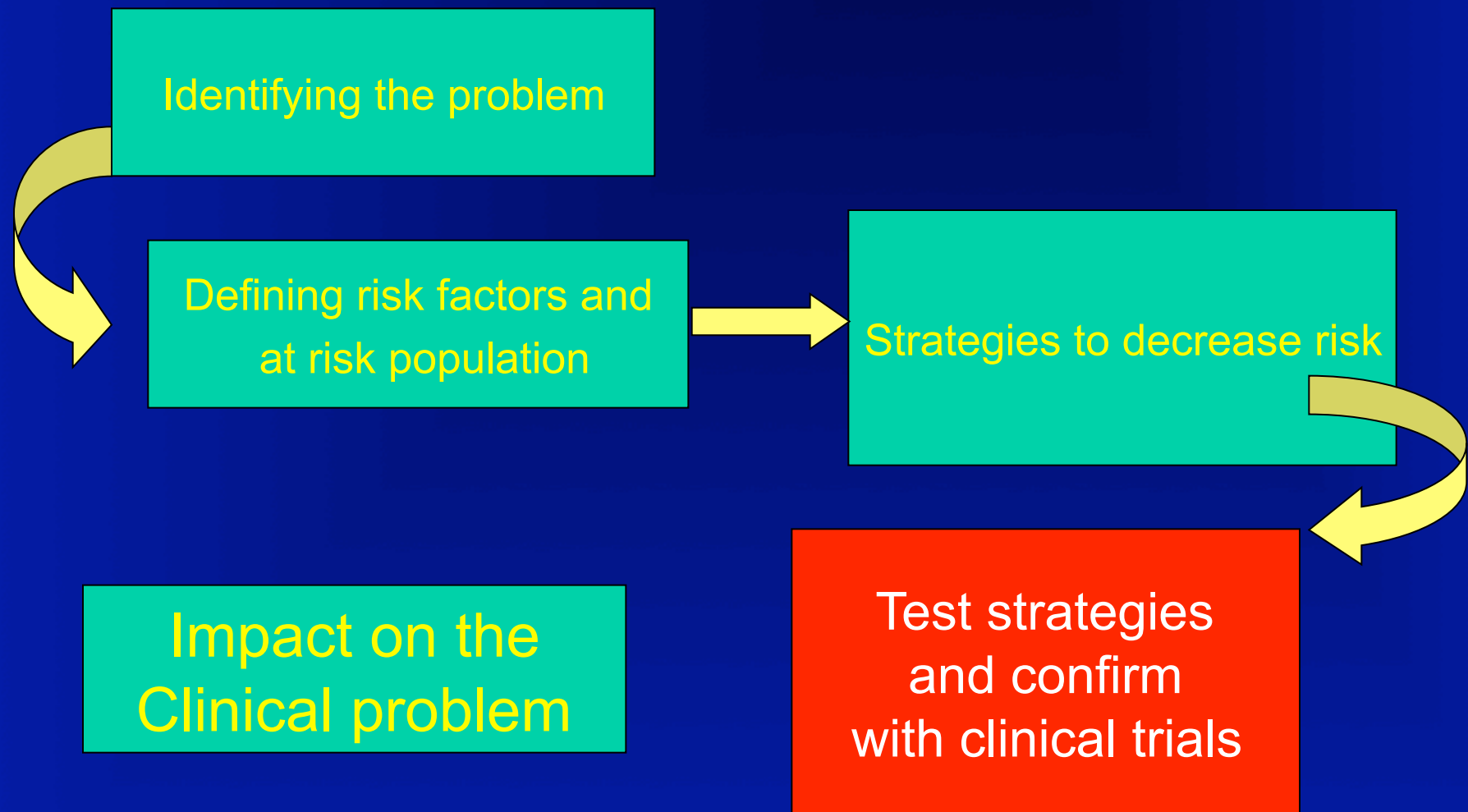
Risk factors for postoperative and persistent pain after surgery



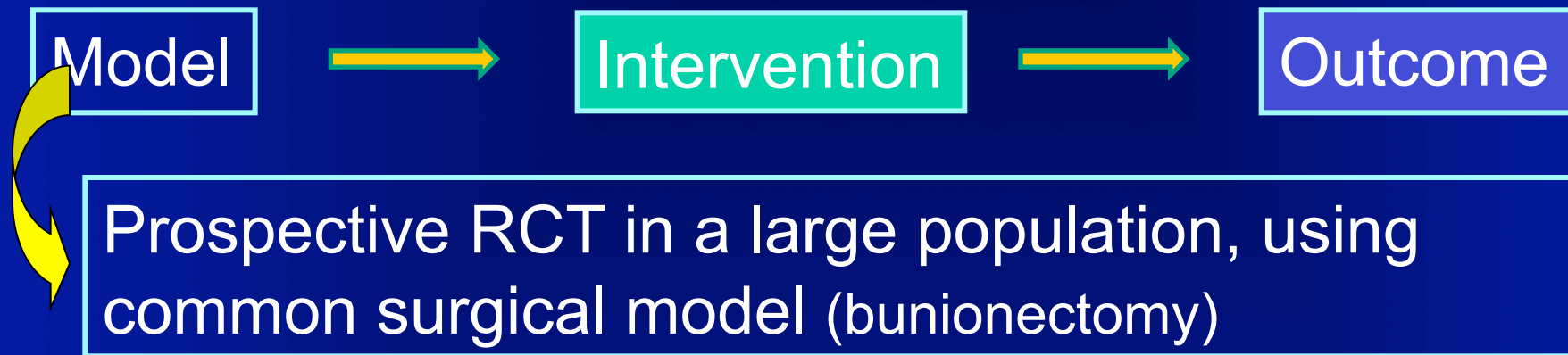
Optimizing Postoperative Pain and Recovery



Optimizing Postoperative Pain and Recovery



Strategies to Increase Signal to Noise Ratio!!



OR

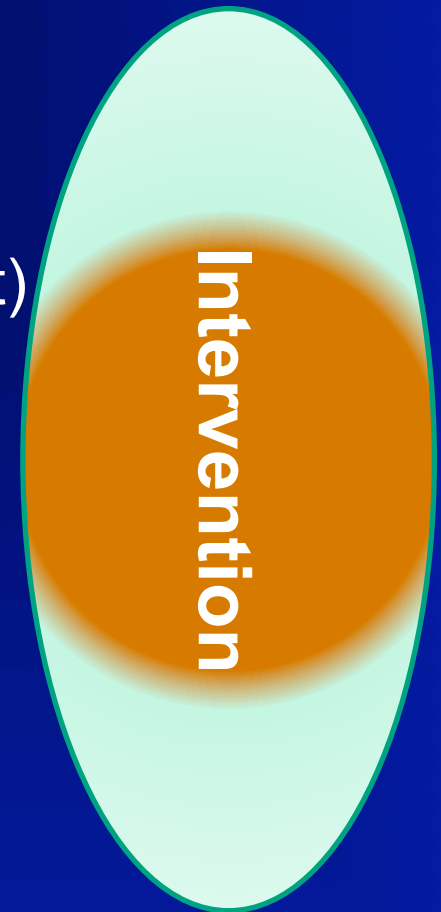
Prospective RCT in an enriched High-risk population

Interventions

- What ?
- When ?
- For how long?

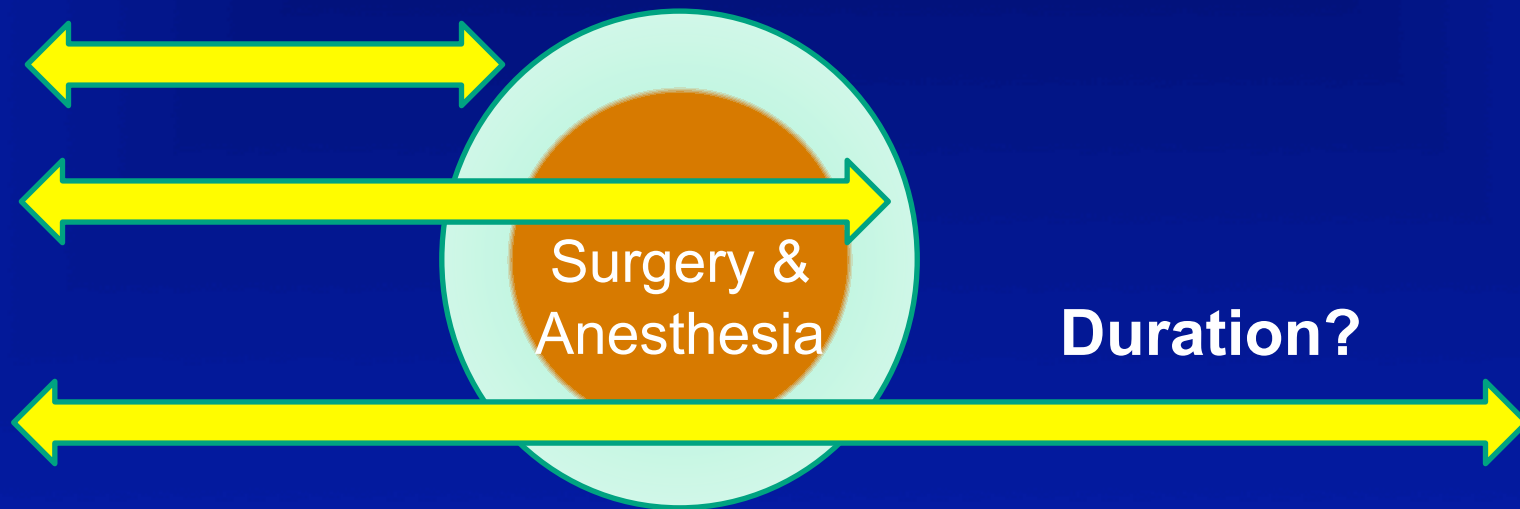
Types of Interventions

- Pharmacologic
 - Single drug (a sole agent), D-R study
 - Combination therapies (an adjuvant)
 - Single dose vs multiple dosing
- Nerve Blocks (long-acting LA)
- Multi-modal analgesia
- Cognitive behavioral therapy

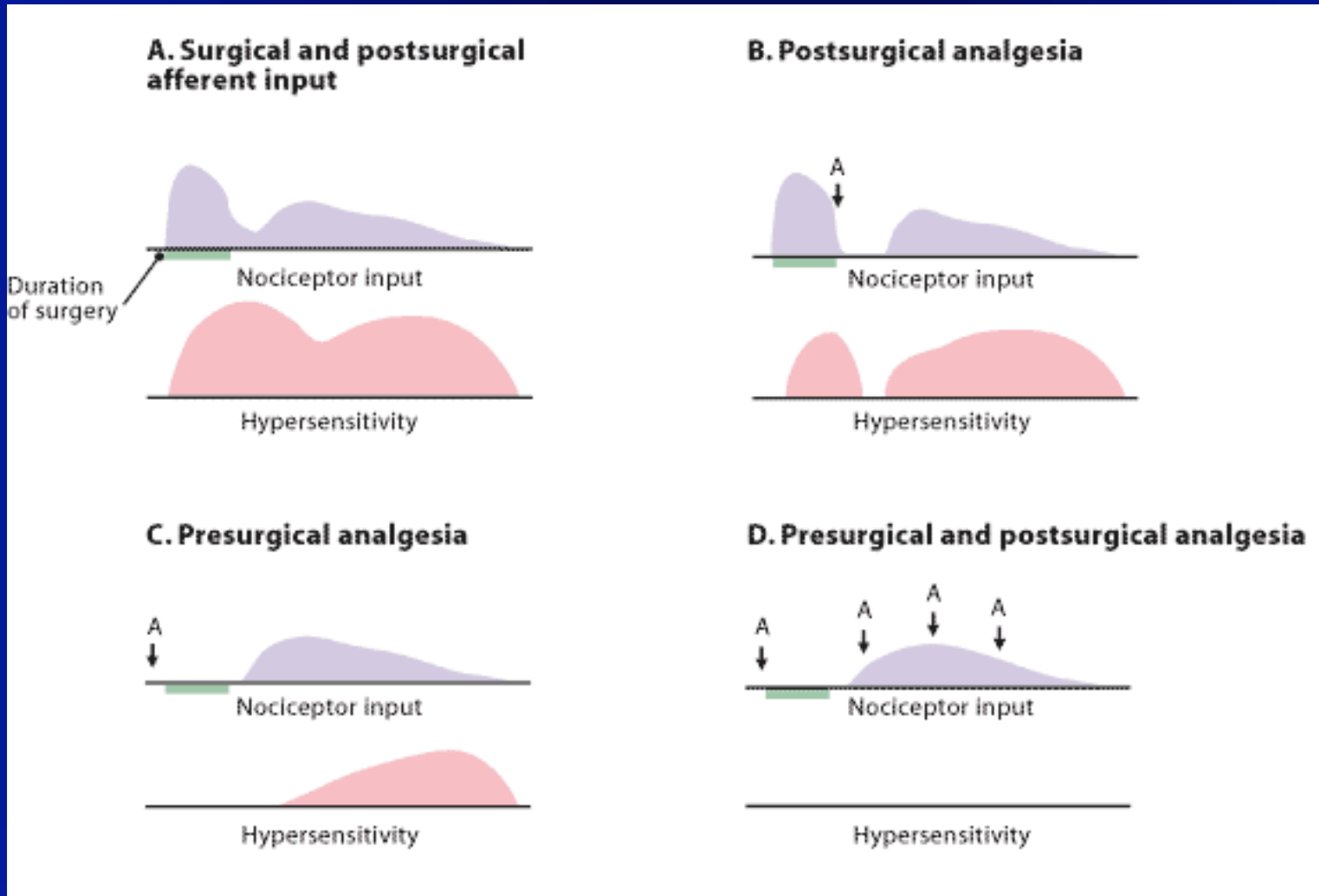


The Timing of the Intervention

- Preoperative: immediate, days
- Pre + Intra-operative
- Pre + Intra + Post-operative



Preventing Surgery-induced Central Sensitization and Hyperalgesia



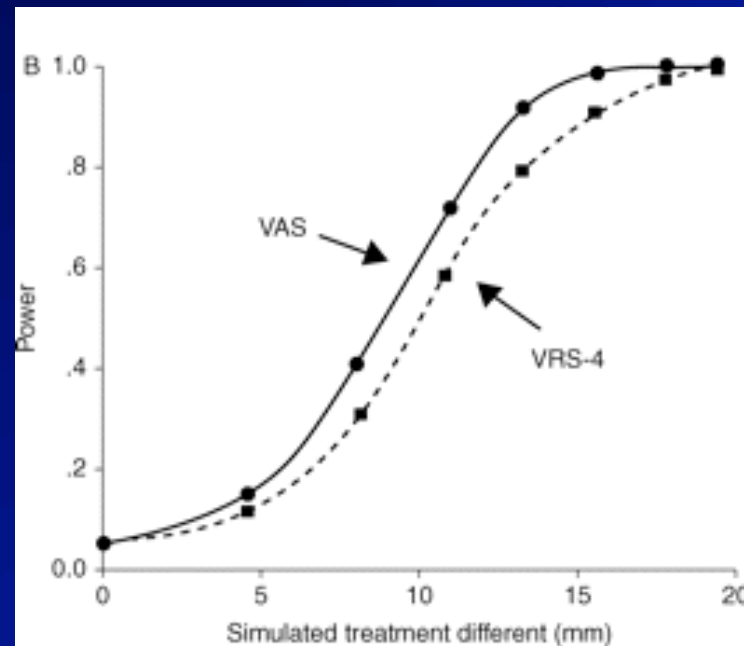
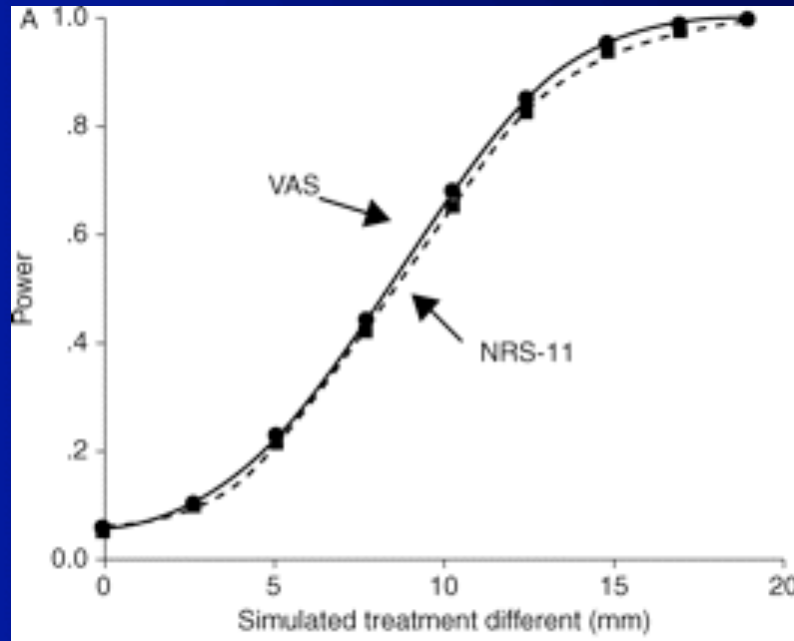
Assessment: Efficacy Outcome Measures-1

- Pain intensity
 - Spontaneous pain
 - Dynamic- movement evoked pain
 - Area under curve: SPID over 48 hr
- Analgesic consumption
- Use of rescue medication

Assessment: Efficacy Outcome Measures-2

- Patient's global satisfaction
- Derived measures: NNT, TOTPAR
- Quantitative Sensory testing:
Hyperalgesia, area of hyperalgesia,
windup response
- Measures of functional recovery
(procedure specific?)

Pain Assessment: Does the scale matter?



Computerized simulation study, random sampling 10,000 times
Simultaneous observations of VAS, NRS and VRS (categorical scale)

Breivik H et al. Brit J Anaesth 101:17-24, 2008
Breivik EK et al. Clin J Pain 16:22-28, 2000

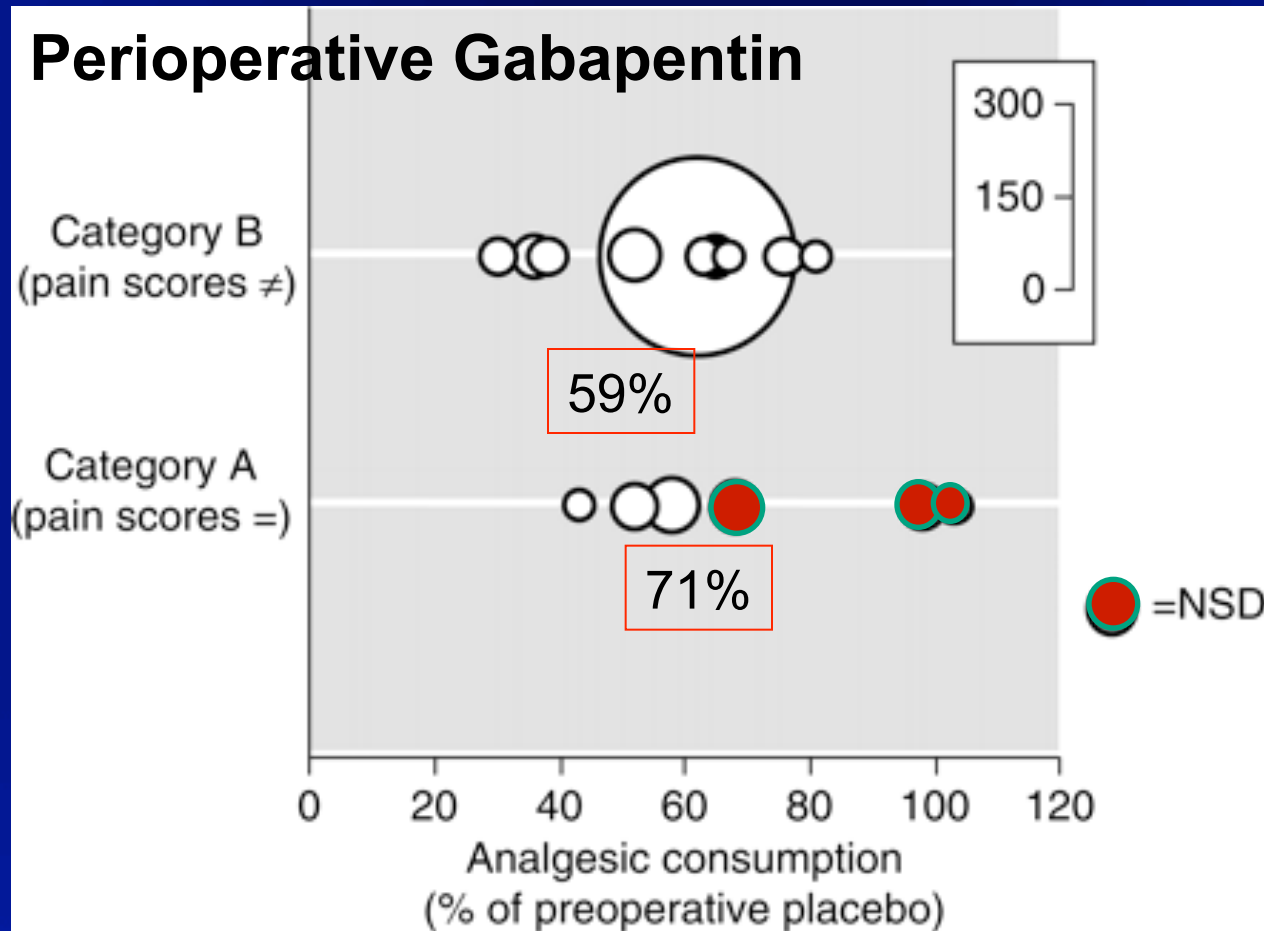
Static vs Dynamic Pain

- Pain during mobilization, deep breathing, coughing more important in reducing postoperative cardio-pulm. complications
- Systemic opioid analgesia provides good comfort at rest but may result in unacceptable side effects at doses required to control movement-evoked pain

Analgesic consumption: Measuring efficacy of combination treatments for postoperative pain

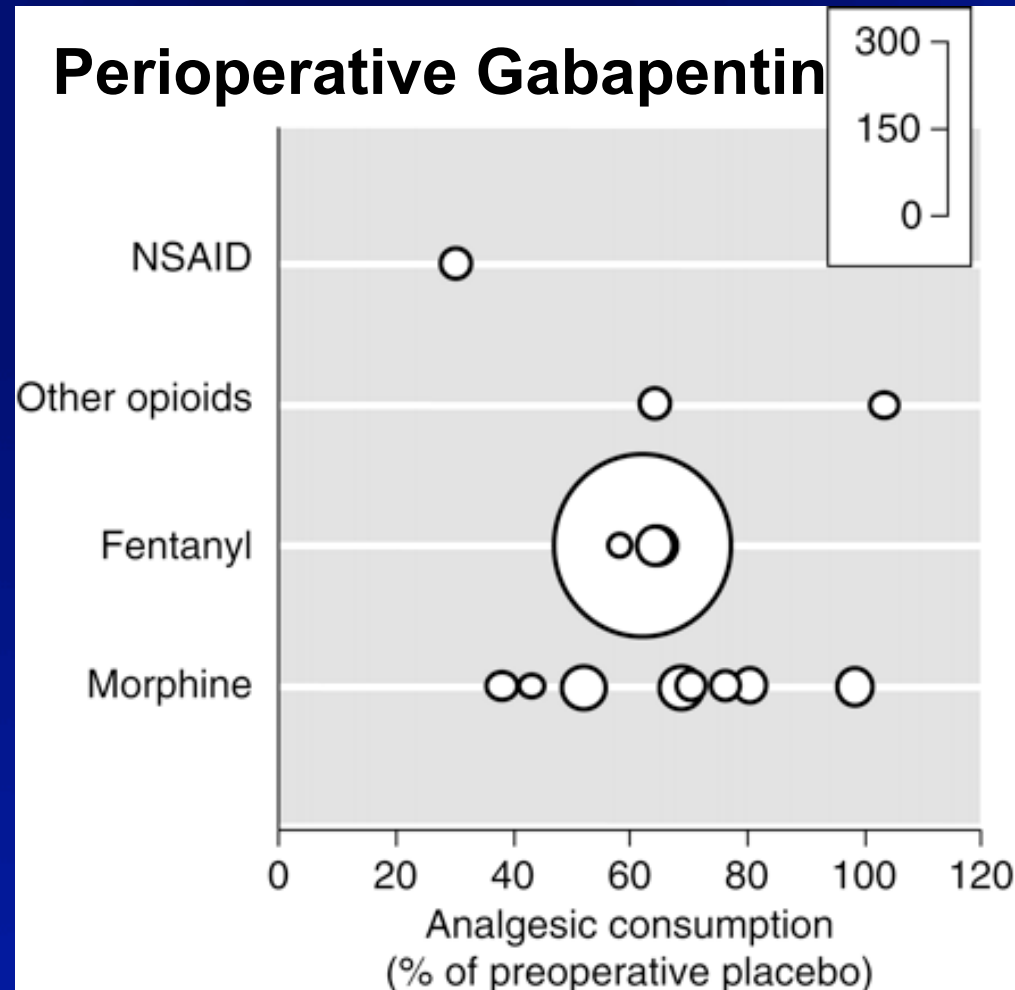
- Measure analgesic consumption using PCA
- **Hypothesis:** an effective intervention should result in lower analgesic consumption than an ineffective intervention
- **Assumption:** patients titrate analgesics to achieve the same state of comfort (pain intensity level) in both groups
- Systematic review of perioperative gabapentin RCTs: similar or dissimilar pain scores

Measuring efficacy of combination treatments for postoperative pain



Measuring efficacy of combination treatments for postoperative pain

Does the postoperative analgesic drug matter?



McQuay et al. Brit J Anaesth 2008;101:69

Postoperative Analgesic Consumption: Confounding factors

- Analgesic consumption might also be influenced by drug side effects- N, V, sedation, effects on cognition, motor dysfunction
- If side effects such as GI and CNS effects limit analgesic consumption, pain scores may be different across groups

IMMPACT recommendations for chronic pain trials: Core domains

- Pain
- Physical function
- Emotional functioning
- Patient ratings of improvement and satisfaction with treatment
- Other symptoms and adverse events
- Patient's disposition & characteristics data

Dworkin et al. Pain 2005;113:9-19

Dworkin et al. J Pain 2008;9:105-21

Assessment: Measures of Adverse Effects

- Postoperative nausea and vomiting
- Postoperative bowel dysfunction
- Postoperative cognitive dysfunction
- Unplanned hospital stay after outpatient surgery
- Length of hospital stay
- Perioperative complications & mortality



Excerpta Medica

The American Journal of Surgery 186 (2003) 472–475
Scientific paper

The American
Journal of Surgery®

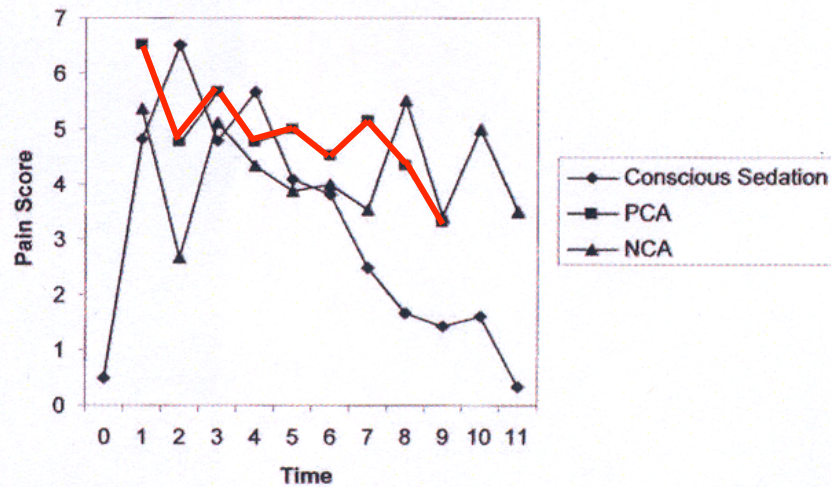
Has the pendulum swung too far in postoperative pain control?

Shiv Taylor, Anthony E. Voytovich, M.D., Robert A. Kozol, M.D.*

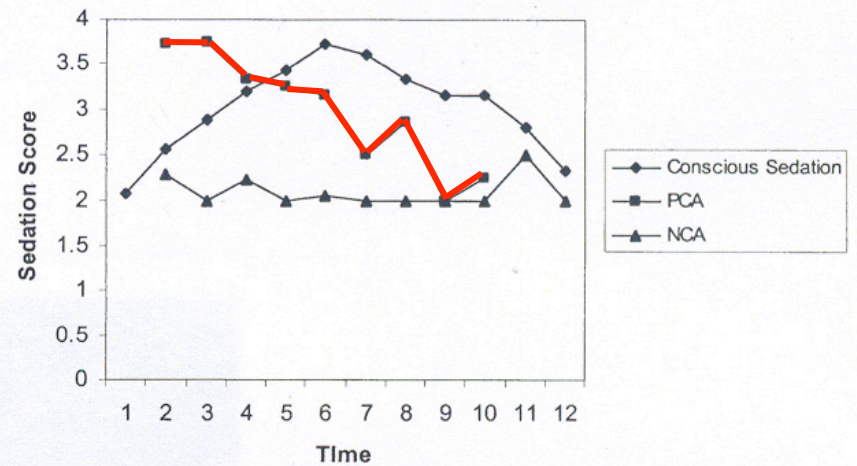
Department of Surgery and Medicine, University of Connecticut School of Medicine, 263 Farmington Ave., Farmington, CT 06030, USA

Manuscript received June 2, 2003; revised manuscript July 24, 2003

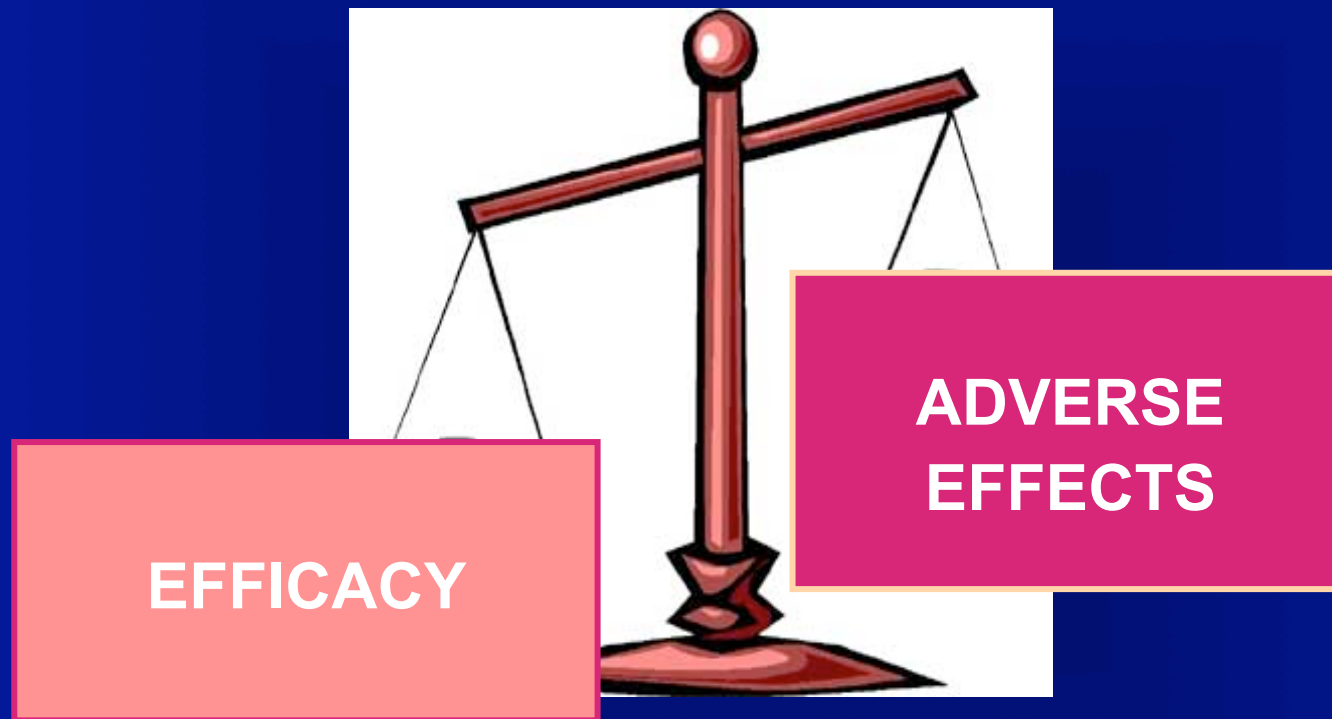
Pain Levels



Sedation Levels

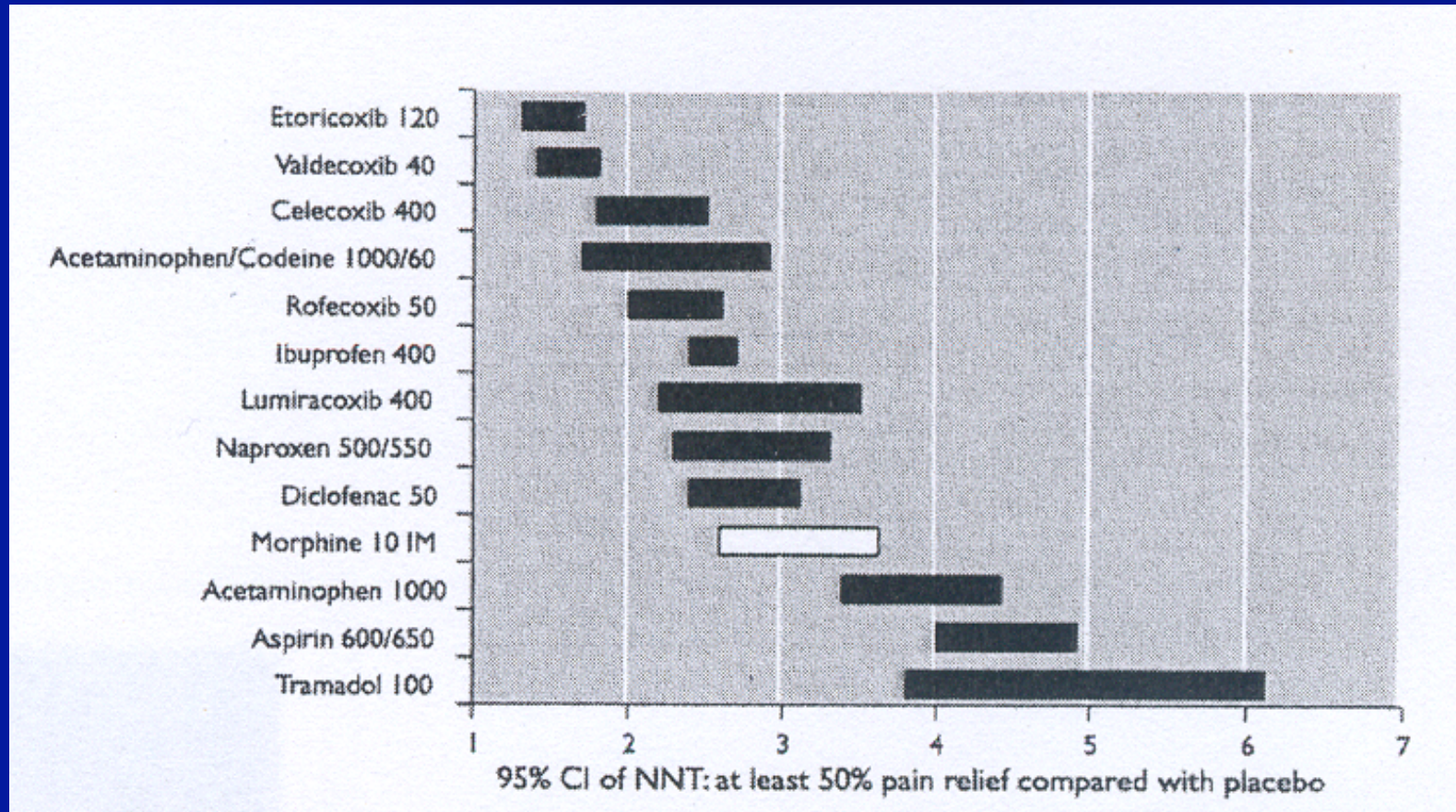


Balance of Efficacy and Adverse Effects in combination trials and comparator studies



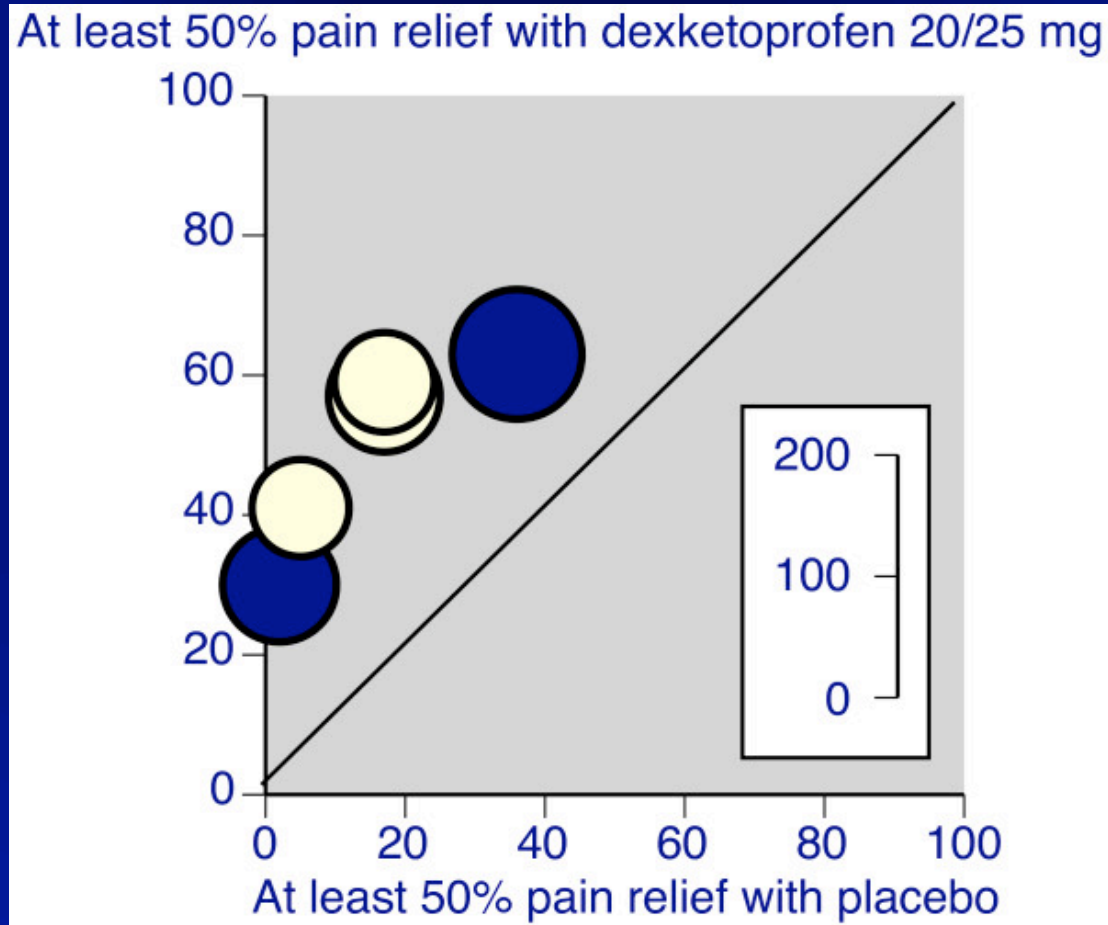
What is a clinically meaningful measure of efficacy?
Should we be using a composite measure that takes pain scores, analgesic use, and adverse effects into consideration?

Relative analgesic efficacy in postop pain: NNTs from single dose trials



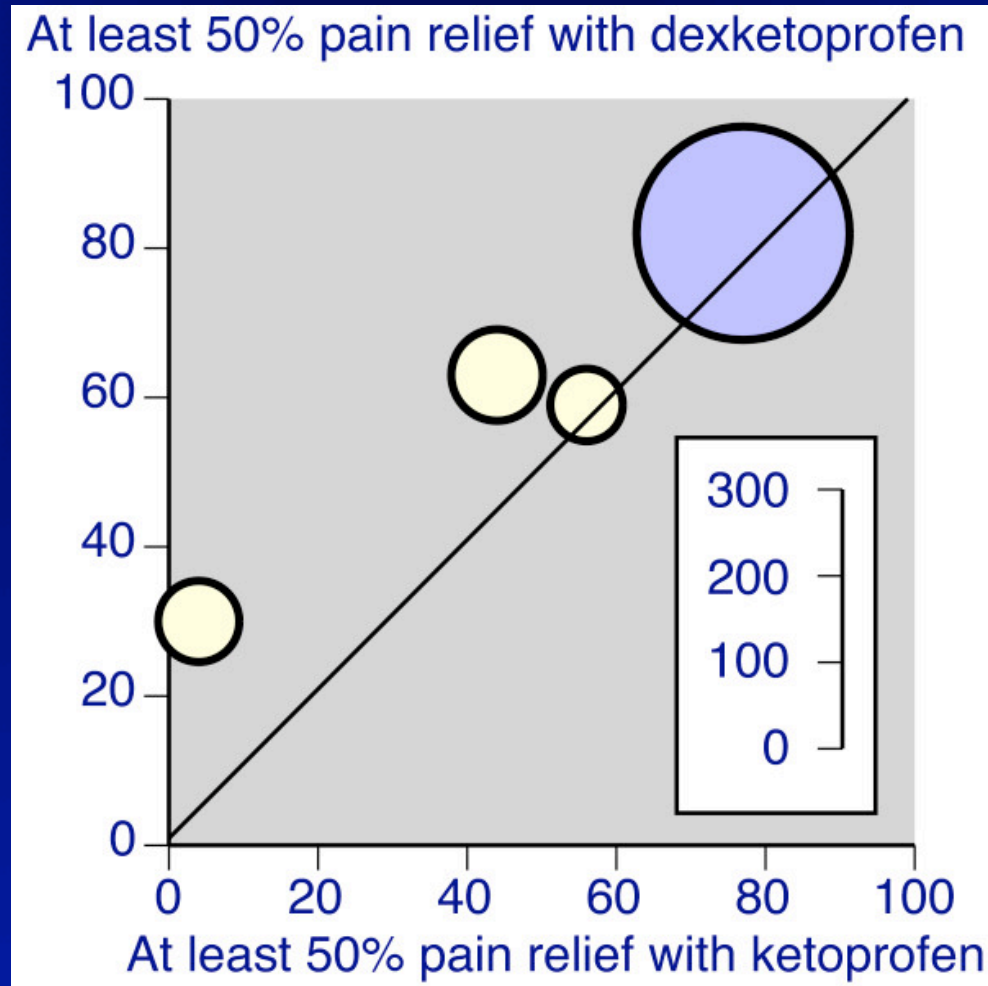
Moertel et al, JAMA 229;55:1974
Mcquay H 2009

Comparison group in Efficacy Trials: Drug vs Placebo



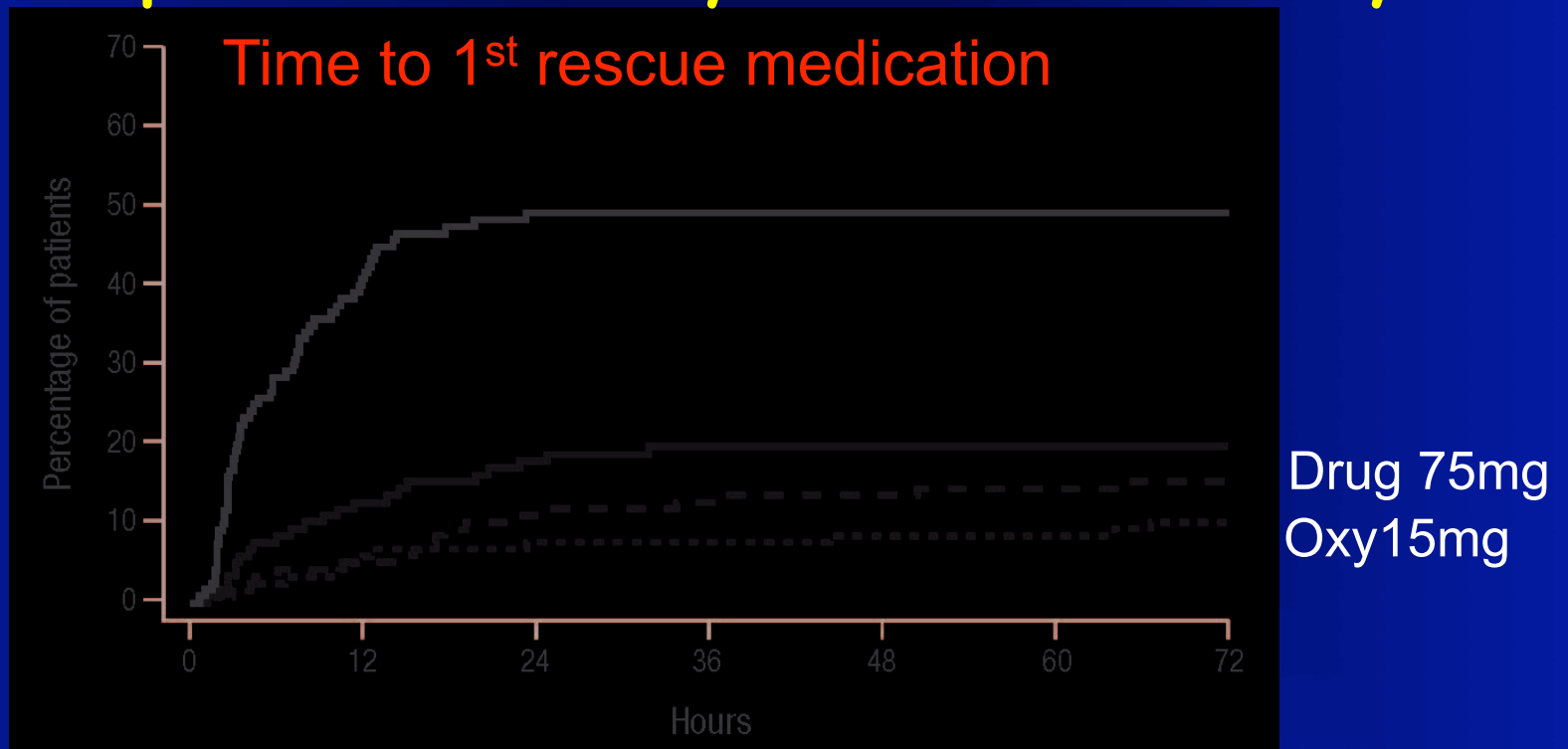
- dental trials
- postsurgical trials

Comparison group in Efficacy Trials: Drug vs active comparator



- 25 mg DK vs 50 mg KP
- 50 mg DK vs 100 mg KP

Dose-response and active comparator study: Bunionectomy



600 pts randomized to 5 groups, regional anesthesia and block
Analgesic efficacy of dose-3 (SPID) similar to Oxy-15, but
incidence of adverse effects lower (postop nausea, vomiting)

Daniels SE et al. 2009

Assessment: Observation Period

- Immediate postoperative period: 6-48 h
- Duration of hospital stay
- Intermediate: 1-3 months
- Prolonged: 6 m- 1 year

Clinical Research at a Crossroads: The NIH Roadmap

“Because treating end-stage disease is so costly, both personally and financially, learning how to pre-empt illness through molecular knowledge and behavioral interventions is the only viable strategy for maintaining the nation’s health in the coming years.”

Persistent Post-surgical Pain"

"Breaking the link .."

Surgery &
Periop. Pain

Chronic
Pain

- 10-50% of pts. have chronic pain post surgery (45 million surgeries/year in USA)
- Surgery contributed to chronic pain in 22.5% of 5130 pts. attending 10 pain clinics in North Britain
- Creation of an iatrogenic disease?

Crombie IK et al., Pain 76;167:1998

Gottschalk A, Raja SN. Anesthesiology 101:1063, 2004

Kehlet et al. Lancet 2006; Katz J & Seltzer Z. Exp Reviews 2009

Incidence of Persistent Postsurgical Pain

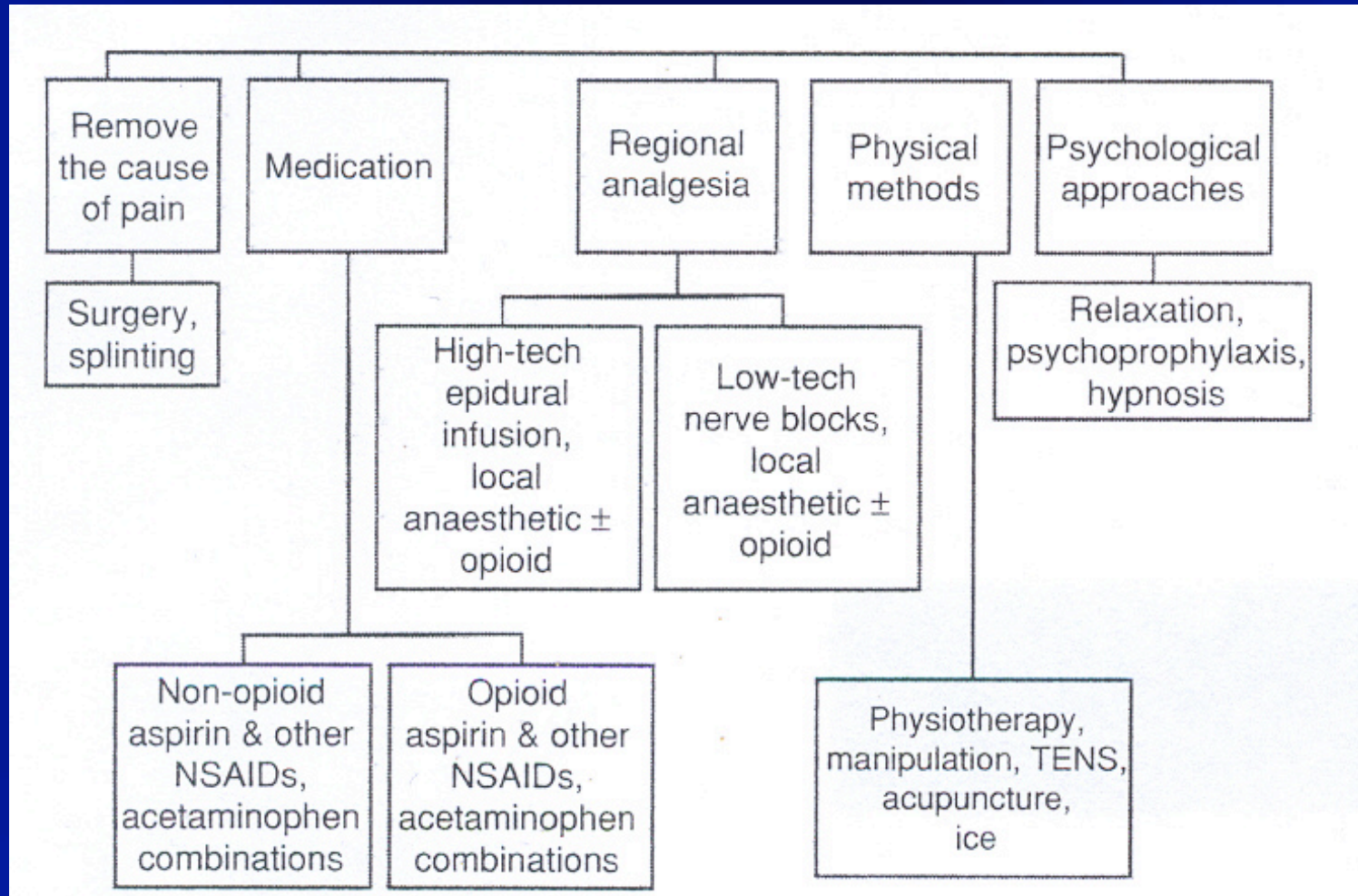
	Estimated Incidence	Pain >5/10
• Amputation	30-85%	5-10%
• Thoracotomy	5-67%	10%
• Mastectomy	11-57%	5-10%
• Ing. Hernia repair	0-63%	2-4%
• C-section	12%	4%
• Cholecystectomy	3-56%	
• Knee arthroplasty	19-43%	
• Hysterectomy	32%	

Optimal postsurgical pain management: Long term benefits

- Higher pain intensity in perioperative period associated with persistent pain
- Intrathecal clonidine and epidural ketamine reduce area of hyperalgesia and decrease incidence of CPSP

Katz J ..1996; Gehling .1999, Nikolajsen .. 1997
De Kock .. 2006, Iohom .. 2005

Complexity of Study Design in the context of multimodal analgesia



Conclusions

- Picking the right model critical- concerns of generalizability
- Studies in select populations needed- elderly, high risk patients
- Duration of intervention- perioperative
- Measure efficacy and adverse effects
- Studies with positive comparators
- Longer term followup and better predictors for preventing PPSP

Strategies for future successes

- Awareness of the clinical problem
- Better collaboration between industry, academia, and regulatory agencies
- Closer interaction between basic and clinician scientists
- Develop better outcome measures
 - Composite measure of desirable (efficacy) and undesirable (adverse effect) effects
 - Measures of functional recovery