Proof of Concept (POC) Studies for Chronic Low Back Pain

REDACTED FOR WEBSITE

Prepared for:

ADEPT

3.25.2011

Southampton, Bermuda

John Markman MD

Associate Professor I University of Rochester School of Medicine

Rochester NY USA

Overview

- Chronic Low Back Pain
  - Surveying a *Methodological Minefield*

- Specific vs. Non-Specific CLBP
  - Who is in your study? Listening to Osler

- Recent Examples from a *Specific* Chronic Low Back Pain Population
  - POC trials for Neurogenic Claudication/Lumbar Spinal Stenosis

PAIN® 149 (2010) 431–434

PAIN®

www.elsevier.com/locate/pain

Topical review

Chronic low back pain analgesic studies – A methodological minefield

R. Andrew Moore [a,*], Sebastian Straube [b], Sheena Derry [a], Henry J. McQuay [a]

[a] Pain Research and Nuffield Department of Anaesthetics, University of Oxford, John Radcliffe Hospital, Oxford, UK
[b] Department of Occupational and Social Medicine, University of Göttingen, Waldweg 37B, D-37073 Göttingen, Germany

- Scant information about CLBP analgesic treatments beyond 6 weeks
- Widely-varying inclusion criteria across 14 trials/11 treatments (*n*=4055)
  - radicular vs. non-radicular (5)
- LOCF analyses with large number of withdrawals (~50% over 12 weeks) means many patients stopping rx for long term problem

In summary, we have no good estimate of effect size or functional impact for drug treatments from valid trials in chronic low back pain (CLBP)

- Moore et al. *Pain* 2010

What is Needed To Navigate the Methodological Minefield?

1) Consensus on the importance of diagnosis (back pain alone vs. back + leg pain)

2) Use of IMMPACT criteria for pain reduction and PGIC

3) Report responders who complete an efficacy phase and meet response criteria (for classic trials) and define LTR for EERW

4) EERW should define and use LTR (loss of therapeutic response as the outcome in the randomization phase

5) Report functional and QoL outcomes

Moore RA, *Pain* 2010

Phase II Proof of Concept Radicular Neuropathic CLBP Analgesic Trials

AUTHOR	YEAR	DRUG	# PATIENTS/ TRIAL	TRIAL DESIGN	OUTCOME
Atkinson et al.	1998	Nortriptyline	11	DB, RCT	Nortriptyline > Placebo
Remmers et al.	2000	Pregabalin	32	Add-on	Pregabalin = Placebo
Remmers et al.	2000	Pregabalin	104	Monotherapy	Pregabalin = Placebo
Medrik-Goldberg et al.	1999	Acute Lidocaine Infusion	30	DB, RCT	Lidocaine > Placebo Lidocaine > Amantadine
Khoromi et al.	2005	Topiramate	29	DB, RCT, Cross Over	Topiramate ≅ Active Placebo
Khoromi et al.	2007	Morphine, Nortriptyline, Combo, Placebo	28	RCT, Cross Over	Morphine, Nortriptyline, Combo =Placebo
Yildirim et al.	2003	Gabapentin	50	RCT, open label	Gabapentin > Placebo
Baron et al.	2010	Pregabalin	217	RCT	Pregabalin = Placebo

Chronic radicular pain appears to differ from PHN and DPN in clinically important ways as demonstrated by diffferential analgesic response

-Khoromi S Pain 6:829-836.
-Khoromi S,.Pain 130:66-75.
-Yildirim K,. J Back Musculoskelet Rehabil 22:17-20
-Baron R, Pain 150:420-427.

Ideal POC Model For CLBP

- High Assay Sensitivity
- Rapid Enrollment
- Short Duration of Patient Participation
- Limit exposure to ineffective therapy or placebo

- Optimize Screening = Identify a Relevant Subgroup
  - Clinical (History/Exam) + Radiographic + Electrophysiologic
- Rapid Enrollment=Highly Prevalence/High Unmet Need/Few Alternatives
- Short Duration of Patient Participation= Episodic Treatment
- Limit exposure to ineffective therapy or placebo= Episodic Treatment/n=1

Neurogenic Claudication

John Markman- Translational Pain Research

Hewitt DJ et al. *Pain* 2011

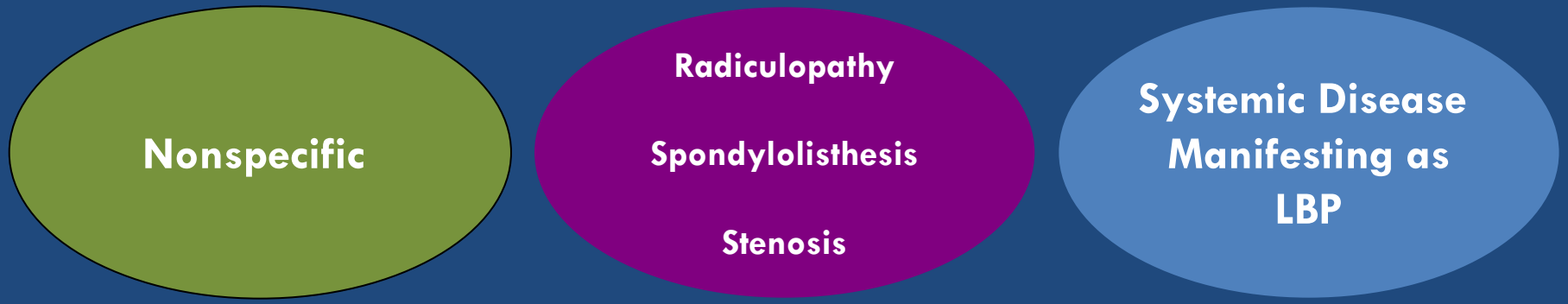
Overview

- Chronic Low Back Pain
  - Surveying a *Methodological Minefield*

- Specific vs. Non-Specific CLBP
  - Who is in your study? Listening to Osler

- Recent Examples from a *Specific* Chronic Low Back Pain Population
  - POC trials from the **LUSTOR** Series Neurogenic Claudication/Lumbar Spinal Stenosis

American College of Physicians/American Pain Society Low Back Pain (**Acute and Chronic**) Classification



85%

Don't Ask/

Don't Tell

Clinical Approach

4%

-Tumor, Infection, CES

-Ankylosing Spondylitis

-Compression Fracture

Chou R et al. *Ann Intern Med* 2007

Low Back Pain (Sub-Groups) vs. Brain Pain (Single Mechanism) Expressed in Your Back

	SPECIFIC	NONSPECIFIC
Mechanism	▪ CLBP reflects activation of peripheral nociceptive pathways due to peripheral tissue injury/inflammation	▪ CLBP reflects plasticity of central nociceptive pathways
Diagnostic Issue	▪ Diagnostic modalities lack sensitivity and specificity	▪ Diagnosis of Exclusion
Therapeutic Issue	▪ Similar and small effects of diverse therapies across a large population	▪ Similar and small effects of diverse therapies across a large population
Favorite Excuse /Secret Hiding Place	▪ Heterogeneous Subgroups / Treatment Matching	▪ Imputation methods for missing data / withdrawal rates

Wand and O'Connell *BMC Musculoskeletal* 2008

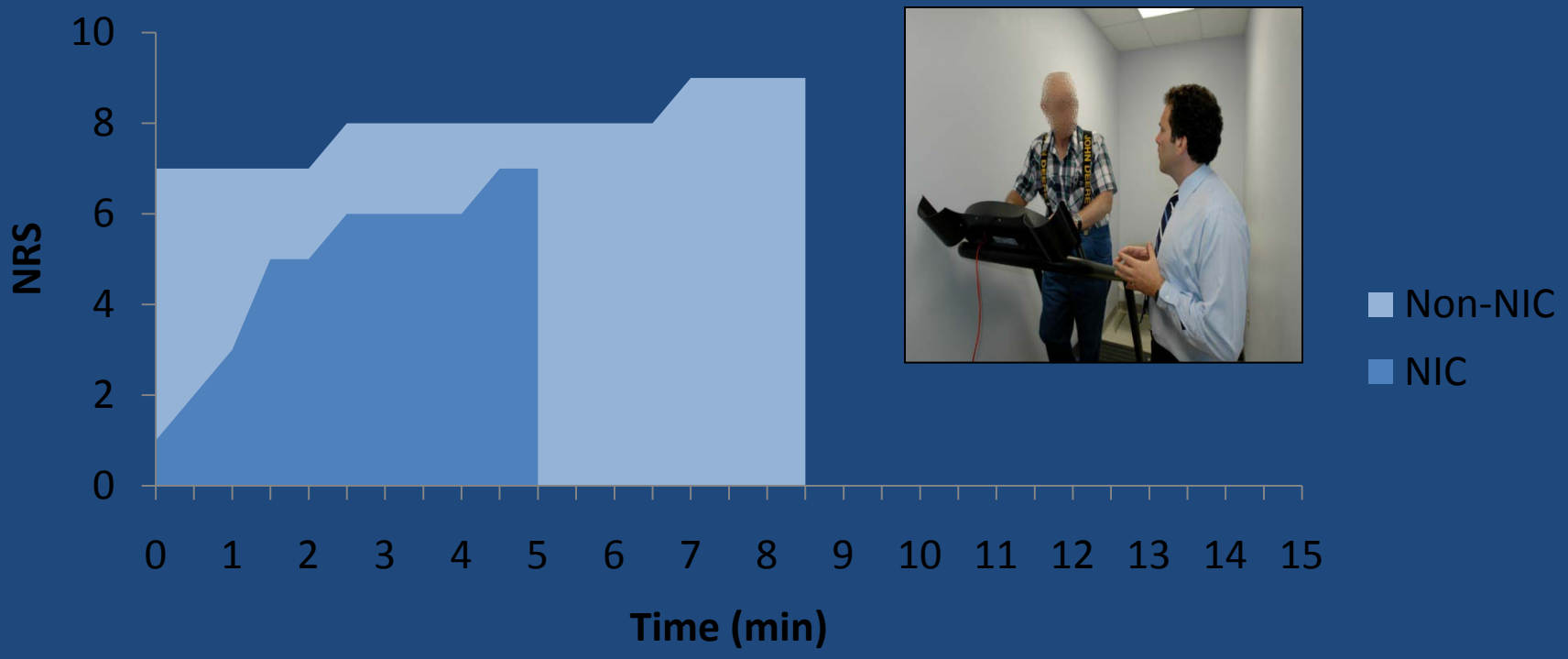
Recent CLBP Analgesic Clinical Trials

AUTHOR	YEAR	DRUG	INDICATION	# PATIENTS	# TRIALS	TRIAL DESIGN	OUTCOME
Vorsanger et al.	2008	Tramadol ER	Back & Leg Pain with Nerve Root Problems	386	1	RCT, Open label	Tramadol ER > Placebo
Vondrackova et al.	2008	Oxycodone/naloxone	Back & Leg Pain with Nerve Root Problems	463	1	RCT, DB, Parallel	Oxycodone/naloxone > Placebo
Webster et al.	2006	Oxycodone/naltrexone	Back & Leg Pain with Nerve Root Problems	719	1	RCT, DB	WD after Randomization
Katz et al.	2007	Oxymorphone ER	Back & Leg Pain with Nerve Root Problems	205	1	RCT, DB	WD after Randomization
a. Skljarevski et al. b. Skljarevski et al.	a. In press b. 2009	Duloxetine	Back & Leg Pain with Nerve Root Problems	640	2	RCT, DB	Duloxetine > Placebo
a. Atkinson et al. b. Atkinson et al. c. Katz et al.	a. 1999 b. 1998 c. 2005	a. Maprotiline & Paroxetine b. Nortriptyline c. Bupropoin	Back & Leg Pain with Nerve Root Problems	225	3	RCT, DB	a. Maprotiline > Placebo & Maprotiline > Paroxetine b. Nortriptyline > Placebo c. Bupropoin < Placebo
a. Birbara et al. b. Pallay et al.	a. 2003 b. 2004	Etoricoxib vs. Placebo	Non-Radicular CLBP	644	2	RCT	Etoricoxib > Placebo
Hale et al.	2007	Oxympophone ER vs. Placebo	Non-Radicular CLBP	347	1	RCT, DB	WD after Randomization
a. Peloso et al. b. Ruoff et al.	a. 2004 b. 2003	Tramadol/acetaminophen vs. Placebo	Non-Radicular CLBP	658	2	RCT, DB	a. Tramadol/acetaminophen > Placebo b. Tramadol/acetaminophen > Placebo

Moore RA, Straube S, Derry S, McQuay HJ Chronic low back pain analgesic studies--a methodological minefield. Pain 149:431-434

Moore RA *Pain* 2010

Treadmill Testing + Radiographic Correlation



	Non-NIC Phenotype	NIC Phenotype
Age	69	66
Gender	Male	Male
Imaging	L3-L4 moderate central canal stenosis; bilateral moderate neural foraminal stenosis	L3-L4, L4-L5 moderate-severe central canal stenosis; bilateral moderate neural foraminal stenosis

Neurogenic intermittent claudication associated with lumbar spinal stenosis often has a distinctive clinical signature.

Cardinal Features

Anatomic Distribution	Lumbar and leg(s)
Temporal Pattern	Progressive
Key Exacerbating Factor	Standing and walking
Key Alleviating Factor	Postures that reduce lumbar lordosis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Surgical versus Nonsurgical Therapy for Lumbar Spinal Stenosis

James N. Weinstein, D.O., M.S., Tor D. Tosteson, Sc.D., Jon D. Lurie, M.D., M.S., Anna N.A. Tosteson, Sc.D., Emily Blood, M.S., Brett Hanscom, M.S., Harry Herkowitz, M.D., Frank Cammisa, M.D., Todd Albert, M.D., Scott D. Boden, M.D., Alan Hilibrand, M.D., Harley Goldberg, D.O., Sigurd Berven, M.D., and Howard An, M.D., for the SPORT Investigators*

The creation of a limited, fixed protocol for nonsurgical treatment was neither clinically feasible nor generalizable. . . We did not assess the effect of surgery versus any specific nonsurgical treatment.

Weinstein *NEJM* 2008

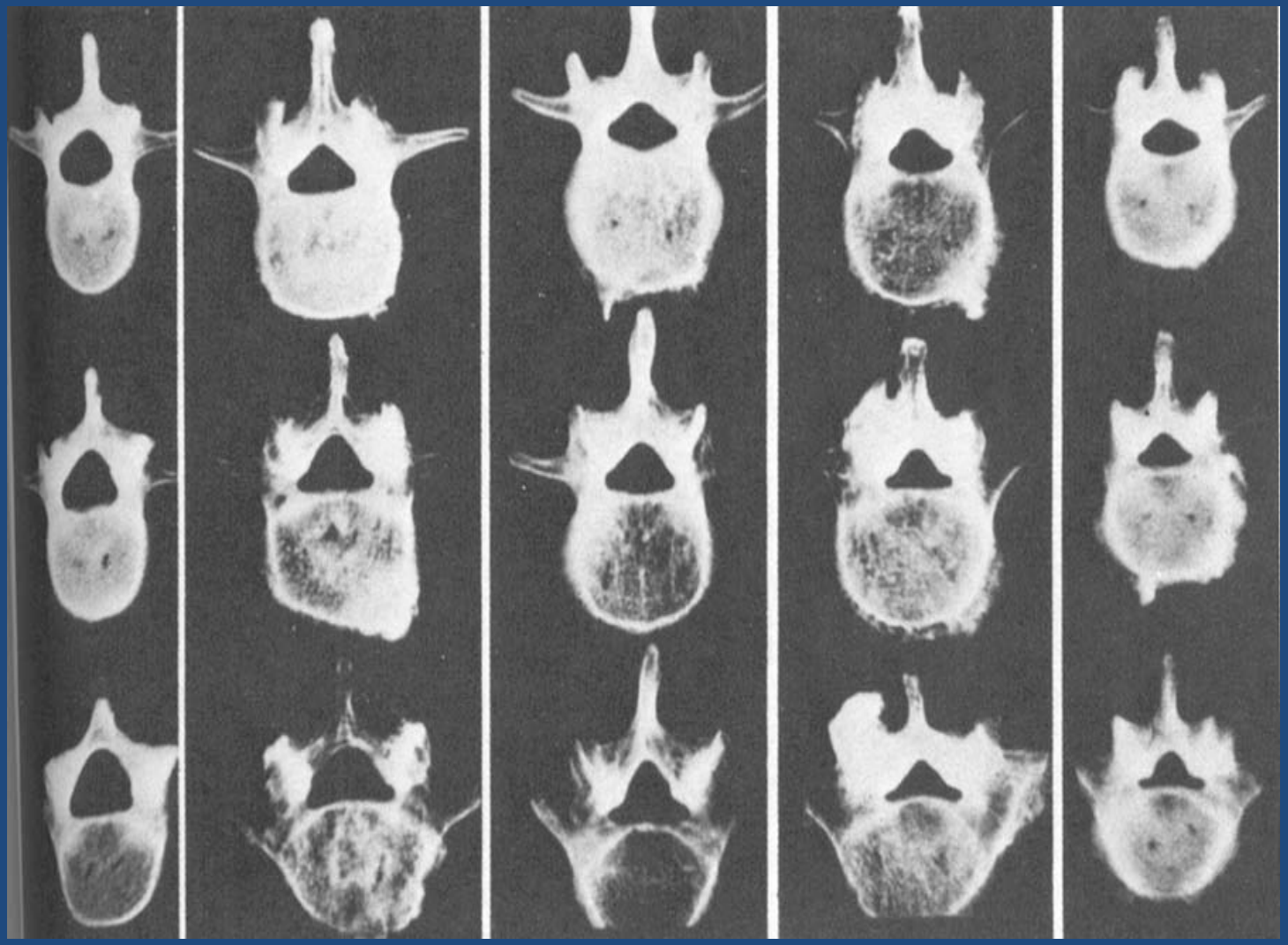
Lumbar Segments with Varying Degrees/Types of Stenosis

Vertebral Segment

L3

L4

L5



Normal Canal Volume

Facet Hypertrophy

Lateral Recess

John Markman- Translational Pain Research

The evolution of the concept of neurogenic claudication

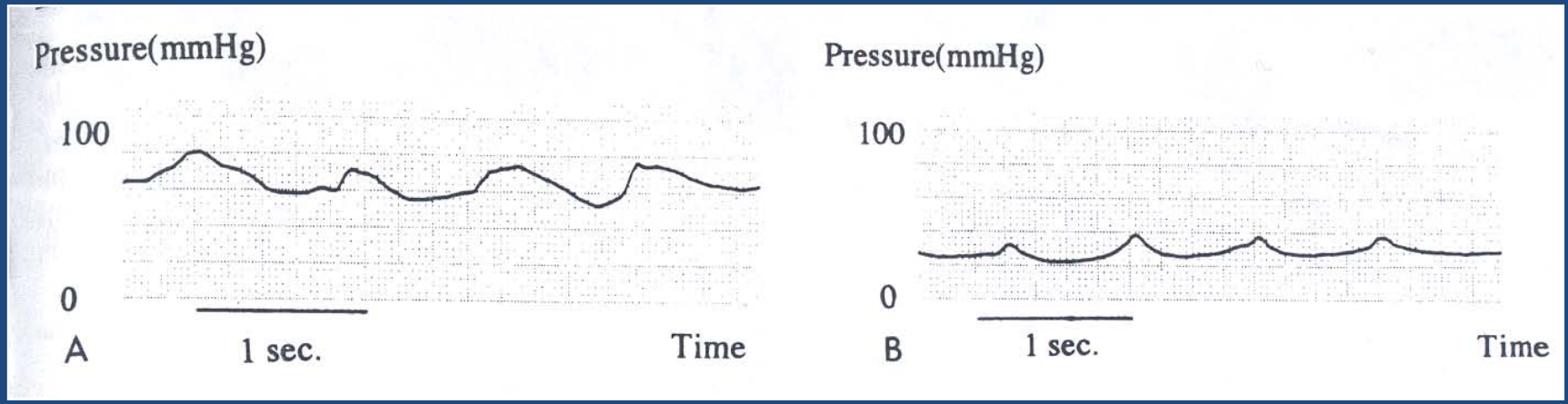
1954 1976 1984 2001 2011

Animal Models

Device (X Stop) approved with neurogenic claudication endpoint

Pathophysiology (Human): Increased epidural pressure in ambulating patients with LSS/NIC

Simple walking	Walking with lumbar flexion

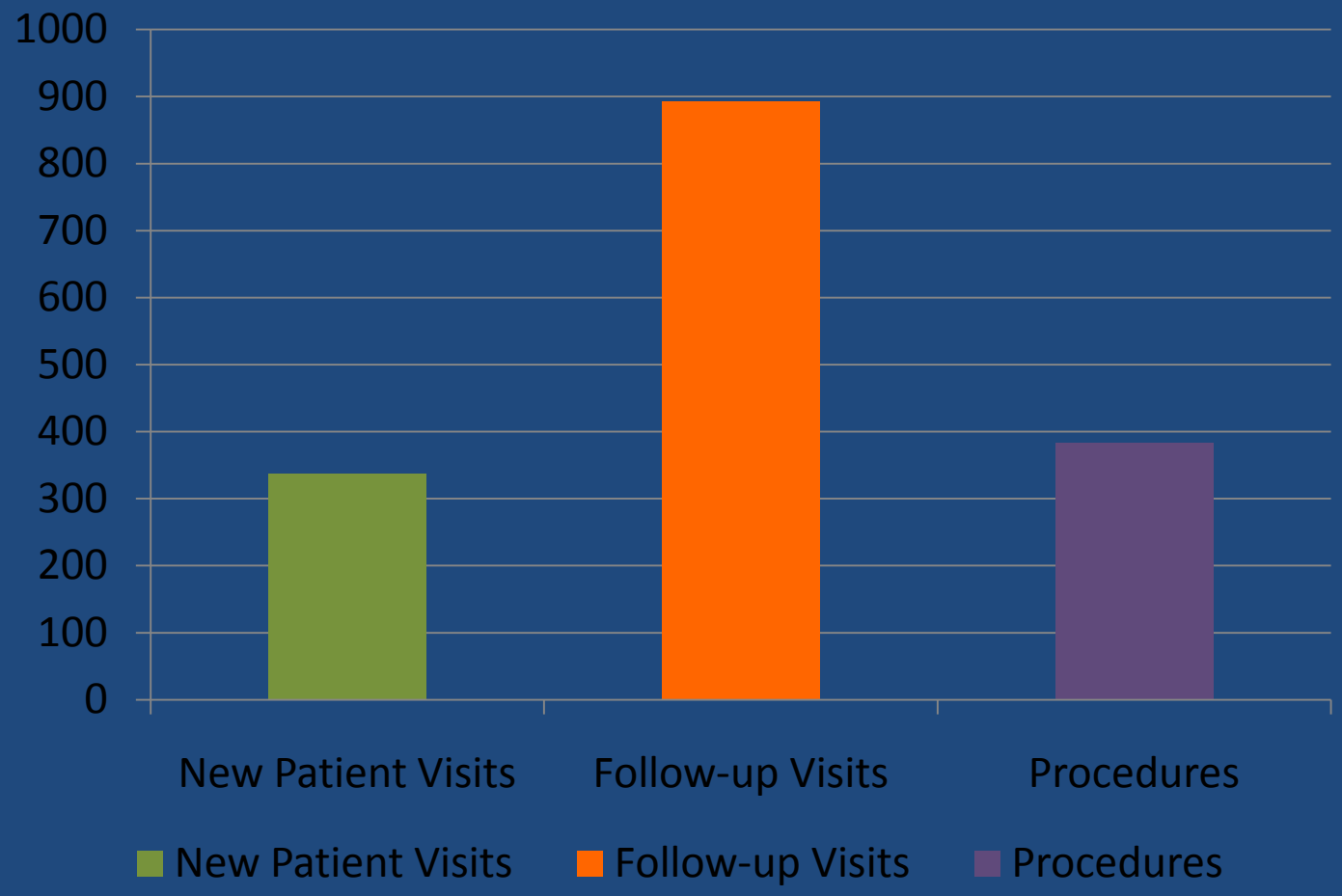


Peak values 82.8+/-14.2	Peak values 34.2+/-4.9

There was no statistical difference between simple walking in normal individuals and walking with lumbar flexion in patients with lumbar spinal stenosis

Takahashi K et al. *Spine* 1995;20:2746-2749

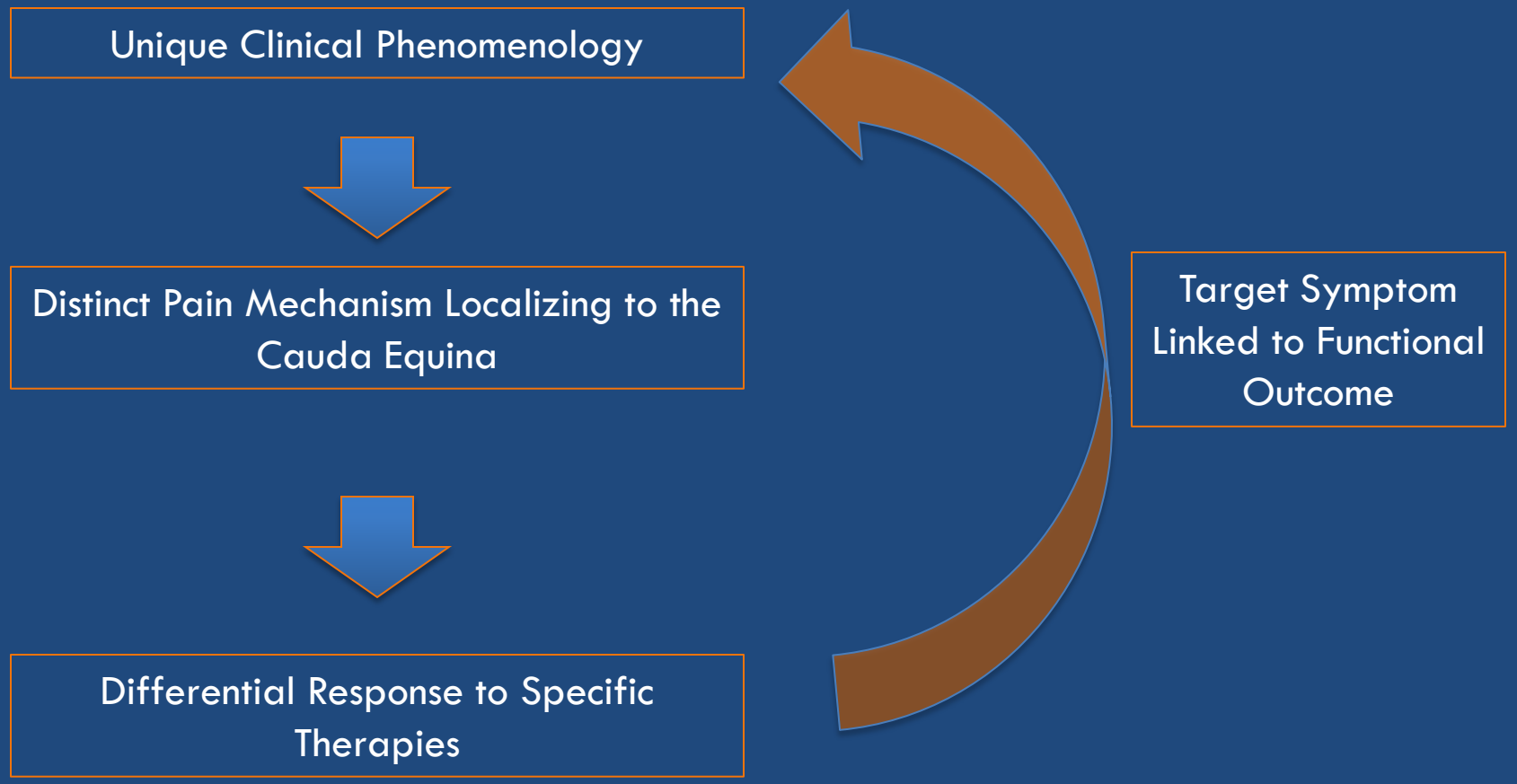
LSS Cases (ICD9 filter) evaluated and treated over 6 month period (6 month/2010)



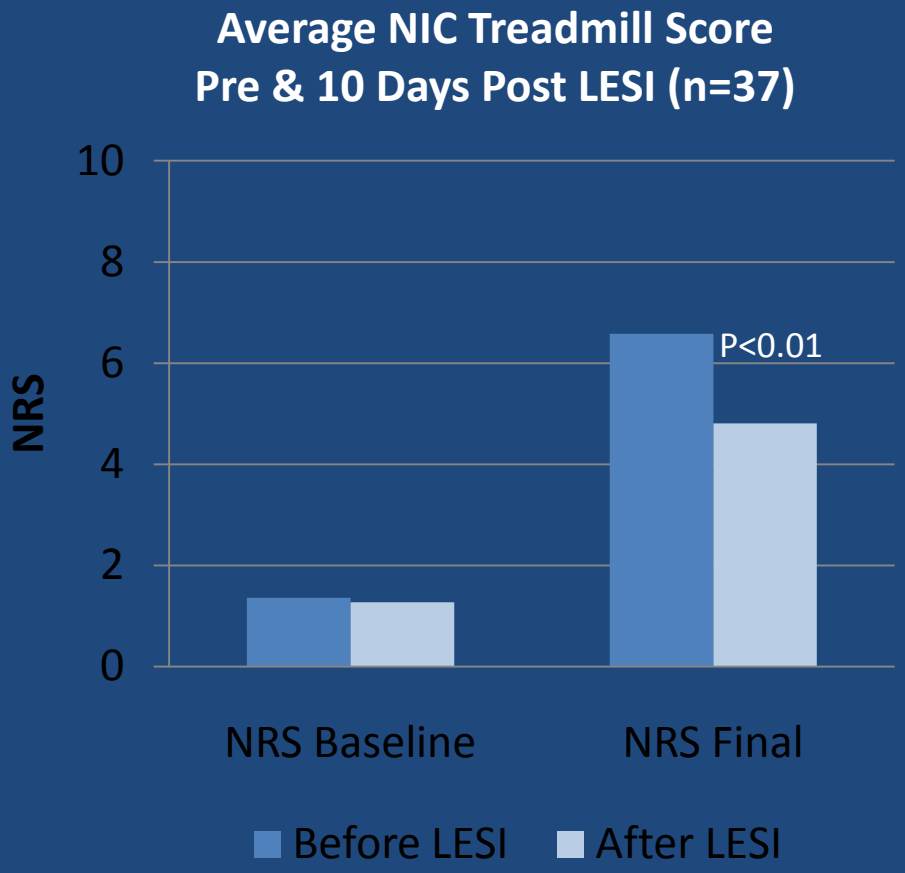
The Target Symptom of Neurogenic Claudication

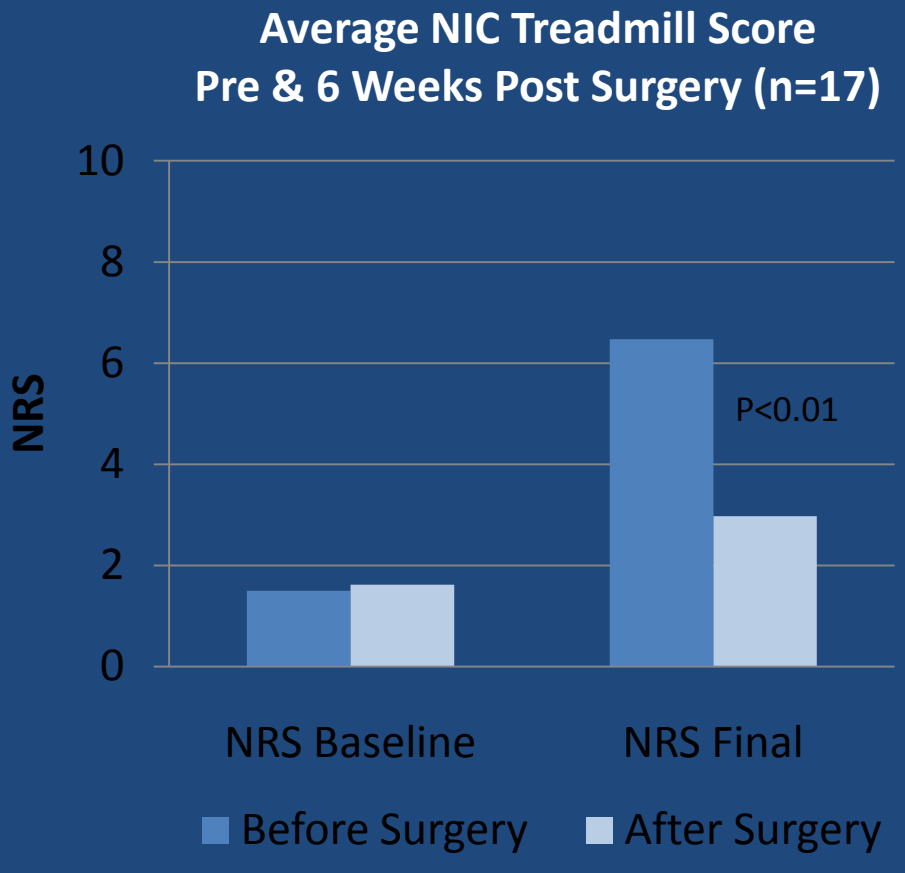
- Distinctive clinical phenomenology
  - Evoked Pain Symptoms
  - Inducible Pain Symptoms
- Radiographic Correlate
- Well Developed Functional Implications
  - MCIC
- Highly Prevalent (*Even a segment of the total CLBP population eclipses the prevalence of more commonly studied chronic neuropathic syndromes*)
- High Unmet Need (no drug with demonstrated analgesic benefit)
- Motivated Study Population

Why Choose Lumbar Stenosis/Neurogenic Claudication as a CLBP POC model?



Decompressive Laminectomy and Epidural Steroid Injection Cohorts from the Clinical Outcomes Project





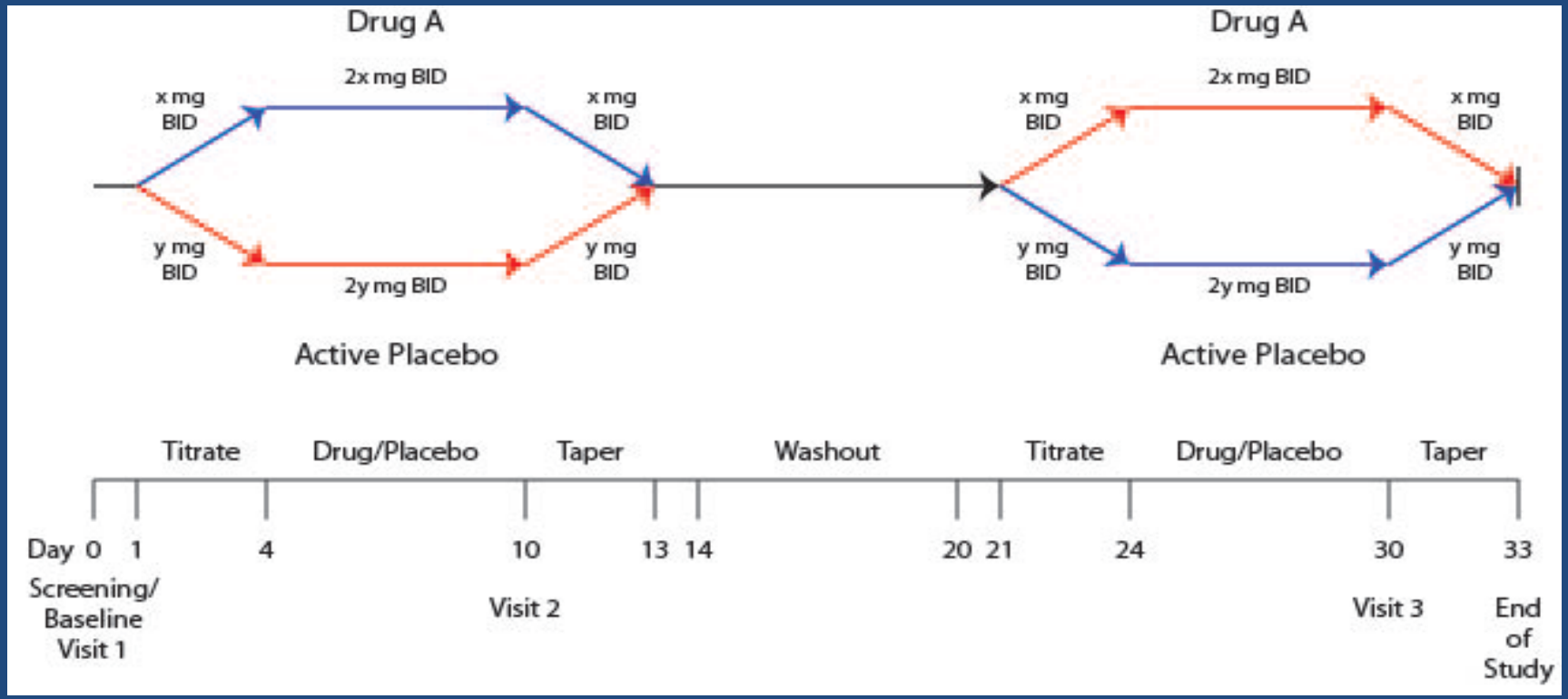
Overview

- Chronic Low Back Pain
  - Surveying a *Methodological Minefield*

- Specific vs. Non-Specific CLBP
  - Who is in your study? Listening to Osler

- Recent Examples from a *Specific* Chronic Low Back Pain Population
  - POC trials from the **LUSTOR** Series Neurogenic Claudication/Lumbar Spinal Stenosis

LUSTOR *X* Study Design: Two Period Crossover



- 1° Objective: Evaluate the effect of active drug in prolonging the time to onset of pain of moderate intensity in patients with neurogenic intermittent claudication
- 2° Objective: Evaluate the functional benefit of active drug with respect to improvement in duration and distance of walking tolerance.
- 3° Objective: Validate treadmill-based methodology for assessing the analgesic efficacy of drugs for neurogenic claudication

Screen Fail Causes

Total # Screened	Total # Enrolled	Total # Screened with Radiographic LSS	Total # Screened Unconfirmed LSS (No Imaging)
196	29	136	31

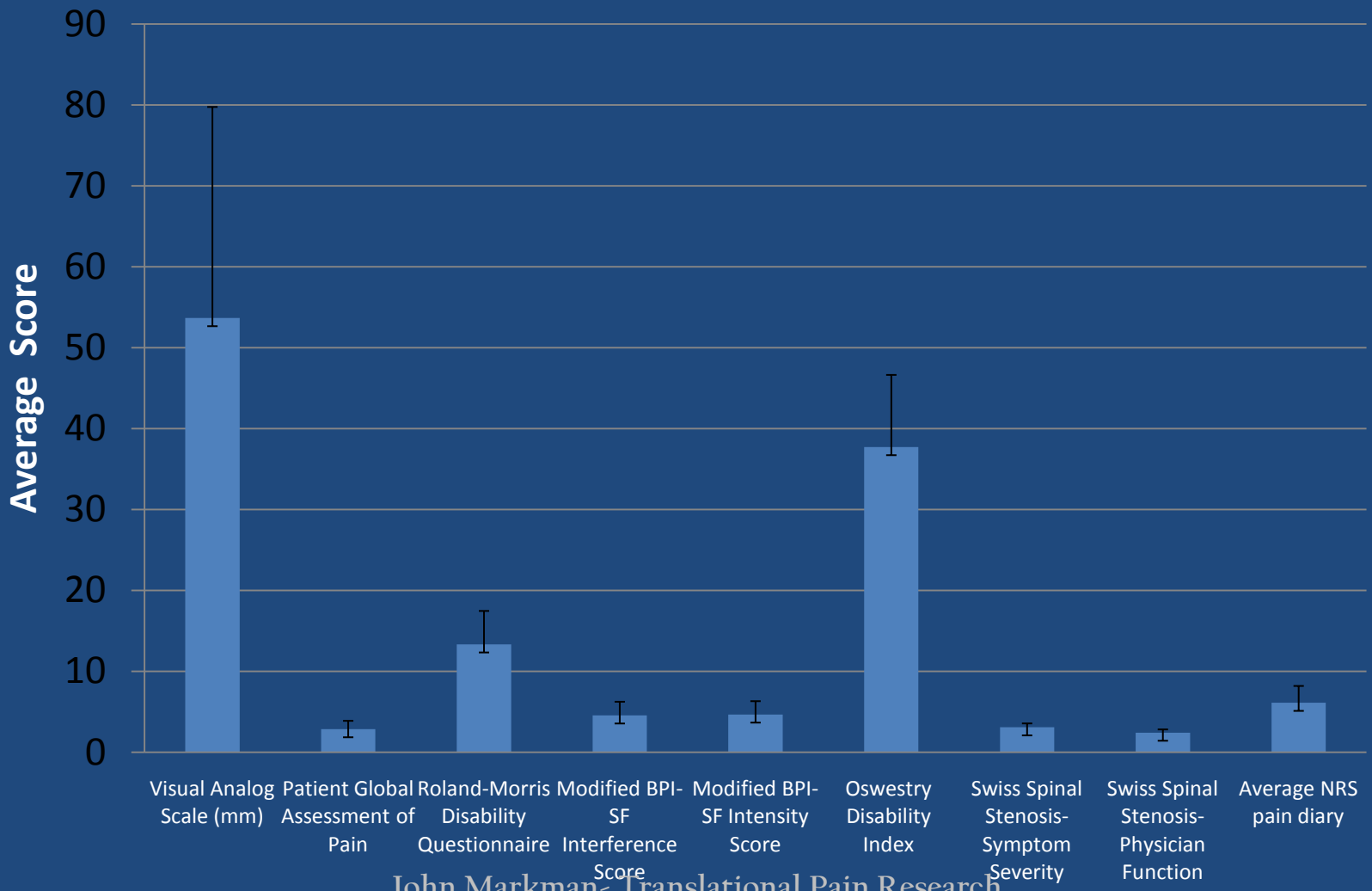
Exclusion Criteria	# Failed Screening with LSS
High rest pain	46 (33.8%)
Not interested	31 (22.8%)
Insufficient pain intensity	23 (16.9%)
Recent LESI or Surgery	17 (12.5%)
On excluded meds	13 (9.6%)
Other	6 (4.4%)

*21 out of 47 (44.7%) *LUSTOR Z* patients previously had or were currently taking study drug at the time of screening.

Patient Demographics and Baseline Characteristics

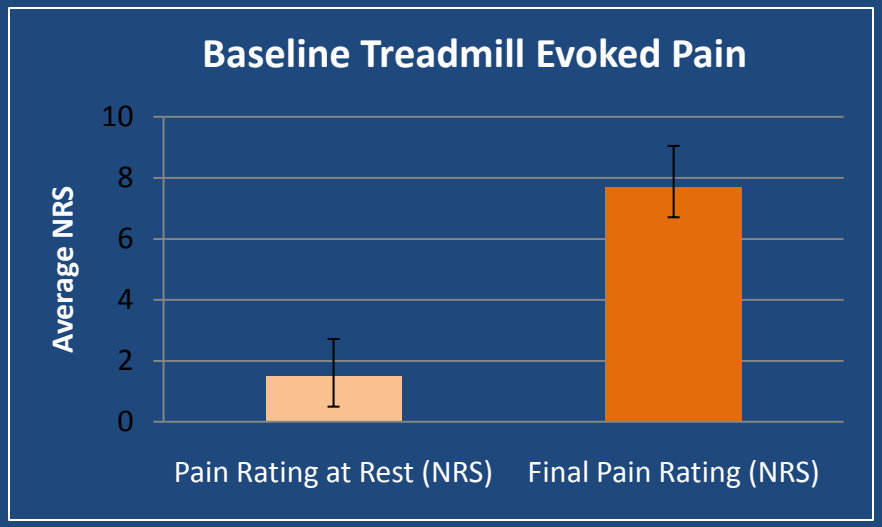
	Number	Percentage
Gender		
Male	20	68.97
Female	9	31.03
Race		
White	28	96.55
Black	1	3.45
Duration of Symptoms		
3-6 months	3	10.34
> 12 months	25	86.21
	Mean	**SD**
Age		
Male	67.85	8.13
Female	73.67	7.25
BMI		
Male	32.13	5.48
Female	32.06	4.14

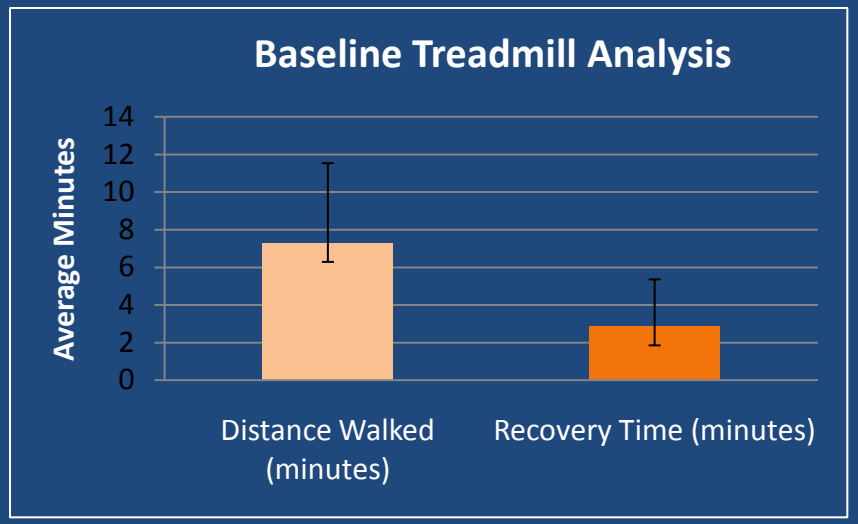
Baseline Questionnaire Assessment (n=29)



Baseline Questionnaire Analysis

Baseline Pain Questionnaires (n=29)	Mean	(SD)
Visual Analog Scale (mm)	53.66	26.09
Patient Global Assessment of Pain	2.86	1.03
Roland-Morris Disability Questionnaire	13.34	4.13
Modified BPI-SF Interference Score	4.56	1.69
Modified BPI-SF Intensity Score	4.67	1.65
Oswestry Disability Index	37.72	8.92
Swiss Spinal Stenosis- Symptom Severity	3.09	0.48
Swiss Spinal Stenosis- Physician Function	2.43	0.40
Average NRS pain diary	6.12	2.08





Baseline Treadmill Assessment (n=29)	Mean	(SD)
Pain Rating at Rest (NRS)	1.5	1.22
Final Pain Rating (NRS)	7.71	1.34
Baseline Treadmill Assessment (n=29)	**Mean**	**(SD)**
Distance Walked (minutes)	7.29	4.25
Recovery Time (minutes)	2.85	2.51

Time to onset of pain (Tfirst (NRS ≥4) @ baseline) for NIC patients (NRS ≤3 at rest, ≥ 6 at final)

Time (min)	Number of Patients
0-3	19 (65.5%)
3-5	5 (17.2%)
5-10*	5 (17.2%)
10-15	0 (0%)

Cohort of NIC Treadmill Patients from Translational Pain Research (n=96)

Time (min)	Number of Patients
0-3	66 (68.8%)
3-5	14 (14.6%)
5-10*	14 (14.6%)
10-15	2 (2.1%)

* Tfirst @ 6 minutes or greater: 4/29 (13.8%); 9/96 (9.4%)

Swiss Spinal Stenosis Questionnaire

	All Treadmill Patients (n=340)	NIC Treadmill Patients (n=137)	LUSTOR Patients (n=29)
Symptom Severity Score	3.16/5	3.05/5	3.09/5
Physical Function Score	2.60/5	2.63/5	2.43/5

- The SSS questionnaire is divided into three sections:
  - The first section evaluates symptom severity on a scale of 1 to 5, ranging from no pain to very severe pain where a score of 5 equals maximum severity.
  - The physical function section uses a scale of 1 to 4, 4 being the most impaired when performing daily activities.
  - Lastly, the satisfaction section is scored within a range of 1 to 4, 4 being the most dissatisfied post-treatment.

Symptom Severity: A score of 3/5 is "moderate" symptom severity

Physical Function: A score of 2.5/5 is "sometimes to always" in pain with physical activity

LUSTOR Z Design