Pain & Pain Medication interactions with cognition

Monique Cherrier, Ph.D.
University of Washington

Definition of Pain

- “an unpleasant sensation associated with a specific part of the body”
- Produced by processes that either damage or are capable of damaging the tissues “noxious” detected by nociceptors
- Nociceptors only respond to noxious stimuli
- Periphery-spinal cord-thalamus-cortex

Transmission & Modulation of pain signal

- Spinal cord- transmission using glutamate (both NMDA & Non-NMDA receptors) and substance P
- Ascending modulation- these signals can be inhibited via mu-opioid receptors
- Descending modulation- norepinephrine (NE) and serotonin (5-HT) act at the site of the dorsal horn to modulate ascending signal (e.g. stress)

Opioid site of action

- Activate the opioid receptors in the midbrain and turn on descending systems
- Activate opioid receptors in the second order pain transmission cells
- Activate terminals of C-fibers in the spinal cord preventing the release of pain neurotransmitters
- Activate opioid receptors in the periphery to inhibit the activation of the nociceptors

Pain Assessment

Please rate your pain by marking the one number that best
Describes your pain at its WORST in the past week

0 1 2 3 4 5 6 7 8 9 10

No
Pain

Pain as bad
As you can imagine

GCPS

Common Clinical Conditions

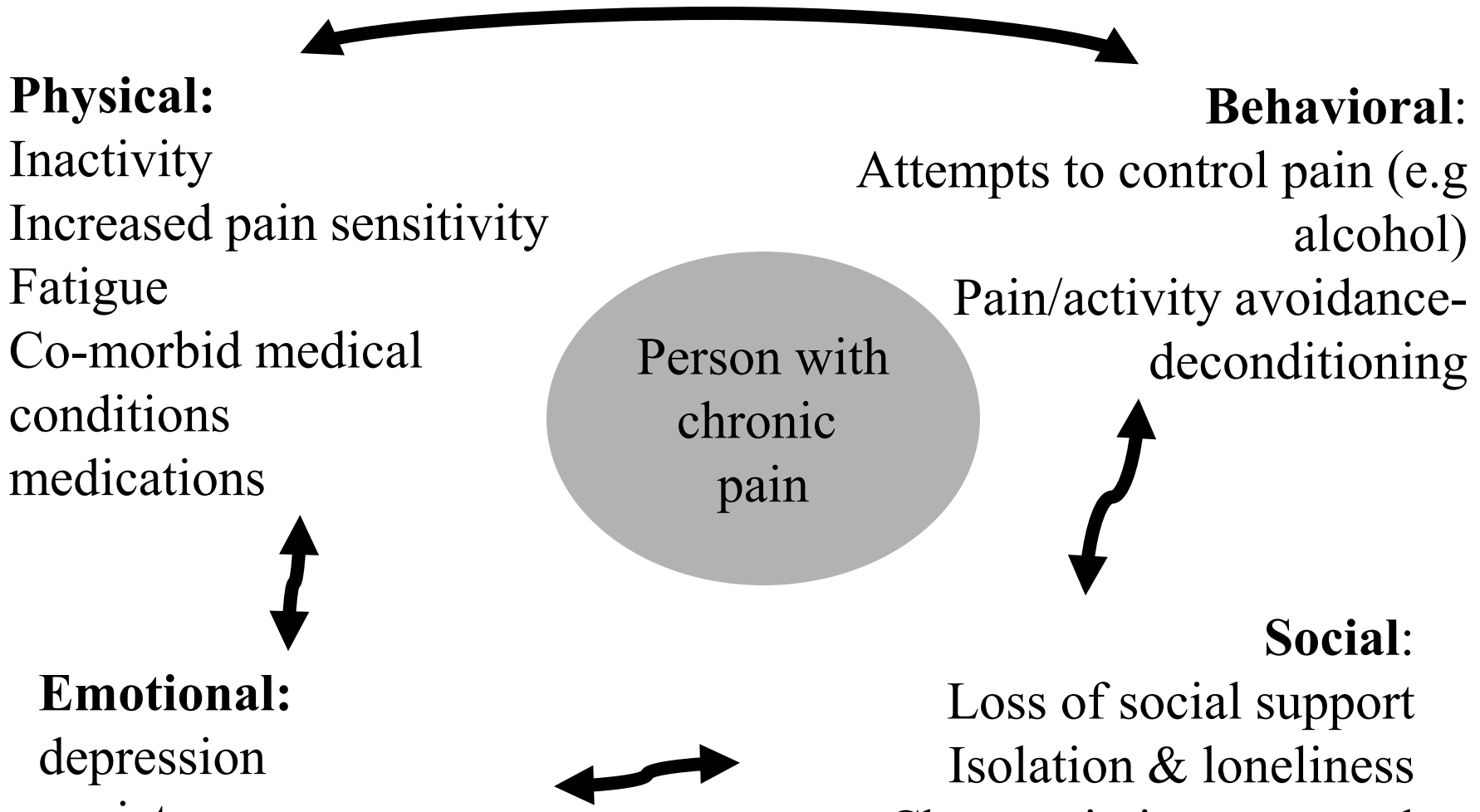
- Cancer
- Hospice
- Chronic back pain
- Post surgery
- Osteo-arthritis & degenerative joint disease
- Vascular
- Headaches
- Fibromyalgia

- NSAIDs
- Acetometaphine
- Opioids
  - methadone
- Amitriptyline
- ~~Cox-2 inhibitors~~

Chronic Pain

- Typically inflammatory or neuropathic and characterized by enhanced perception of pain to a nociceptive stimulus (hyperalgesia) and novel perception of a normally innocuous stimulus as painful
- Spinal cord becomes primed
- Hindbrain facilitates descending activation for hypersensitivity

Bio-behavioral interaction



Common memory complaints by patients with chronic pain

- Flaws referring to books and films
- Forgetfulness
- Handling of everyday things (prospective)
- Flaws about conversations

- Regression analysis indicated that depression (35%), anxiety (6%) and rumination (2%) were best predictors of complaints

Munoz et al., (2005)

Attention, Pain & Stress

- Healthy controls vs chronic low back pain
- Cold pressor test with monitoring of low back and arm tension, blood pressure
- Randomly assigned to:
  - Sensory focus, distraction, suppression, control
- Stress: mental arithmetic
- Recovery

Burns, Emotion (2006)

- Greatest lower paraspinal (LP) increases were in the suppression group
- The CLBP group demonstrated a further increase of LP during the stress condition this did not occur for the controls
- Weakness or pathology in the LP muscles may leave this system vulnerable to stress reactivity
  - Cycle of chronic low level activation of muscle groups through repetitive tasks in stressful jobs – greater exhaustion and mental tension after work which prevents recuperation

Burns, Emotion (2006)

Persistent pain produces stress like alterations in hippocampal neurogenesis and gene expression

- Rats- given acute or chronic inflammatory stimulus to hind paw (pain) or acute or chronic immobilization (stress)
- Chronic pain and immobilization both decreased BrdU stained cells in the hippocampus
- Decreased BDNF and Nk-1 receptor mRNA levels

(Duric, et al., 2006)

NP Performance Chronic Low Back Pain

Measure	Pain-Free N=160	CLBP N=163	P value
RBANS- Im. Mem	103	98	.002
RBANS- Visuosp.	96	95	
RBANS – Lang.	102	99	.004
RBANS- Attent.	105	105	
RBANS- Del. Mem	97	94	.04
Trails B (T score)	53	50	
Grooved Pegboard	45	42	.04
NART-VIQ	98	98	

(Weiner et al., Pain Medicine, 2006)

Relationship of Mood & Pain & Cognition

- Weiner et al. (2006) sample found NP scores correlated with physical performance and pain intensity

- Karp et al. (2006) N=56 (mean age 71 years)
  - Pain severity was associated with greater impairment on number letter switching (r=-.42)
  - This remained sig. After controlling for depression, sleep, medical co-morbidity, opioid use & education

Subjective Assessment of Drug Effect

- OAC (0-4)
- Flushing
- Skin Itchy
- Sweating
- Numb
- Dry mouth
- Carefree
- Vomiting

- OCEC (0-10)
- High
- Floating
- Lightheaded
- Confused
- Pleasant/unpleasant thoughts or sensations
- Drunk

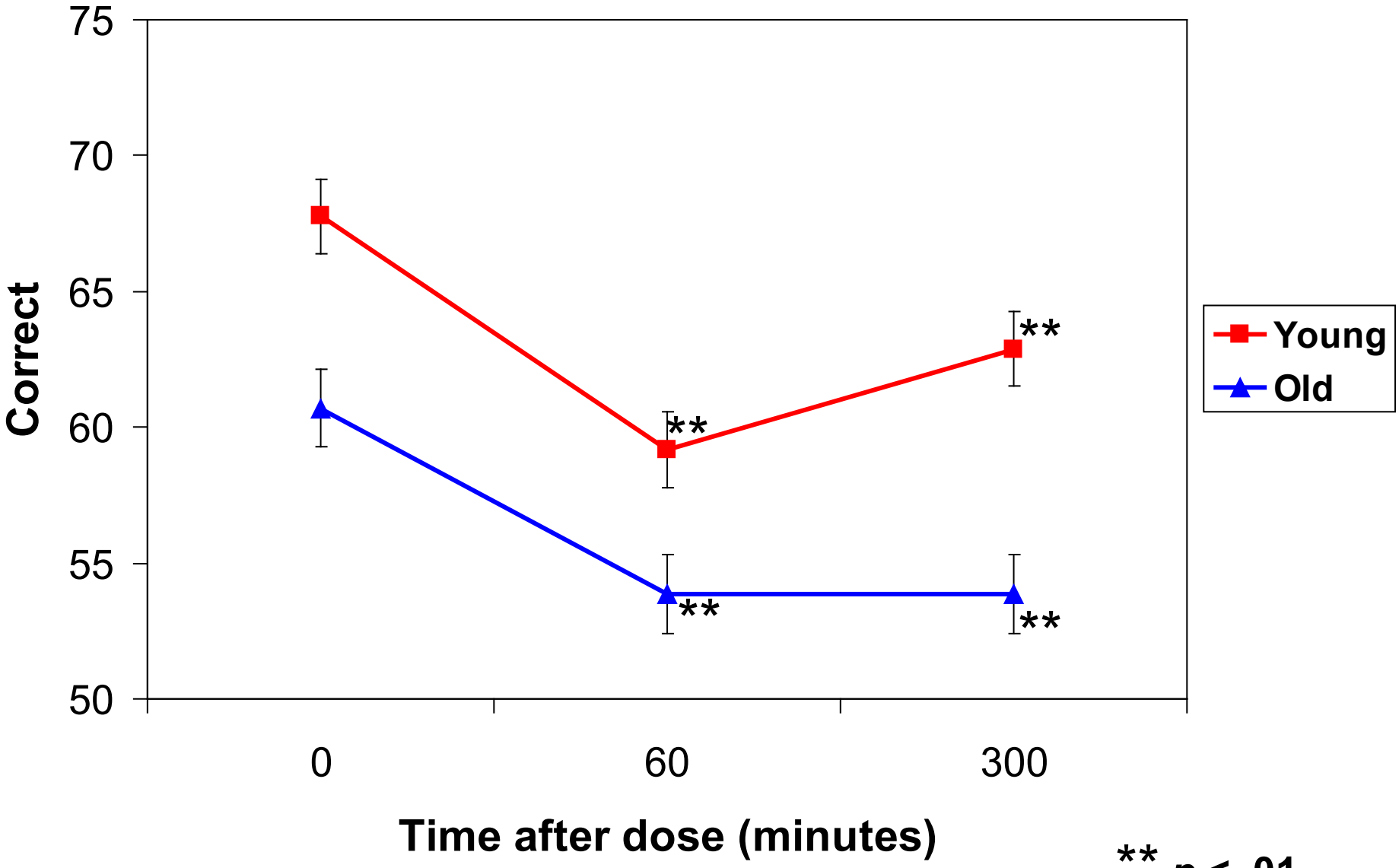
Relationship of Subjective vs Objective Cognitive Performance While Taking Opioids

- Correlation between subjective reports of cognitive impairment and poor performance on neurocognitive tests (Sjogren, 2000)
- No correlation between subjective reports of cognition and actual performance (Cull, 1996; Klepstand, 2002)

Opioid effects in young adults

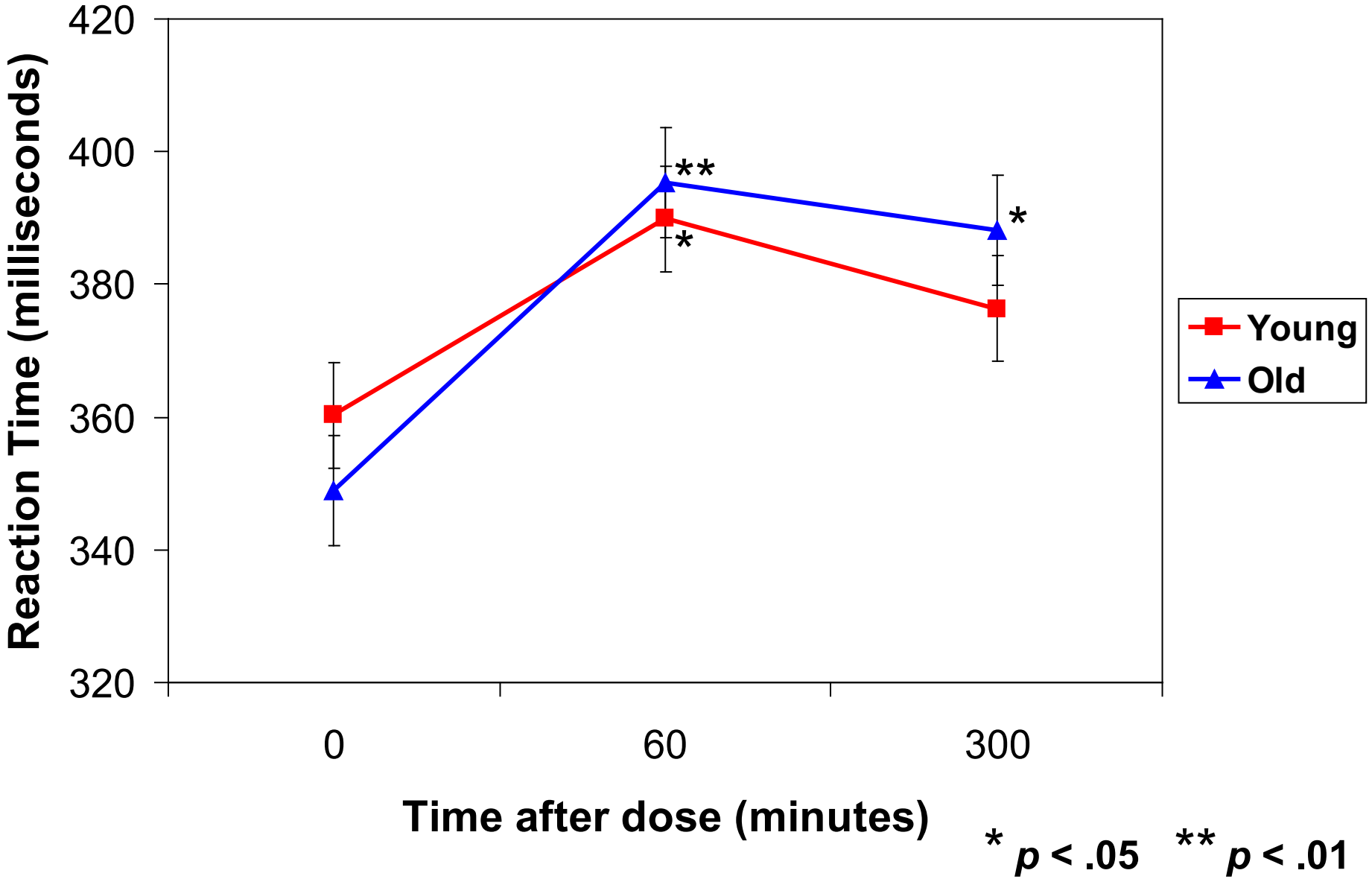
- Single dose IV opioid in young adults- no to minimal cognitive effects (Hill, 2000; Zacny, 1994,1997,1998)
- Oral opioids (e.g. morphine, codeine) have minimal effects on cognition in young adults (Hanks, 1995; Walker, 1998; O'Neill, 2000)
- Cumulative IV doses do demonstrate decreased RT, logical reasoning, concentration, information processing (Walker, 1999)

Digit Symbol



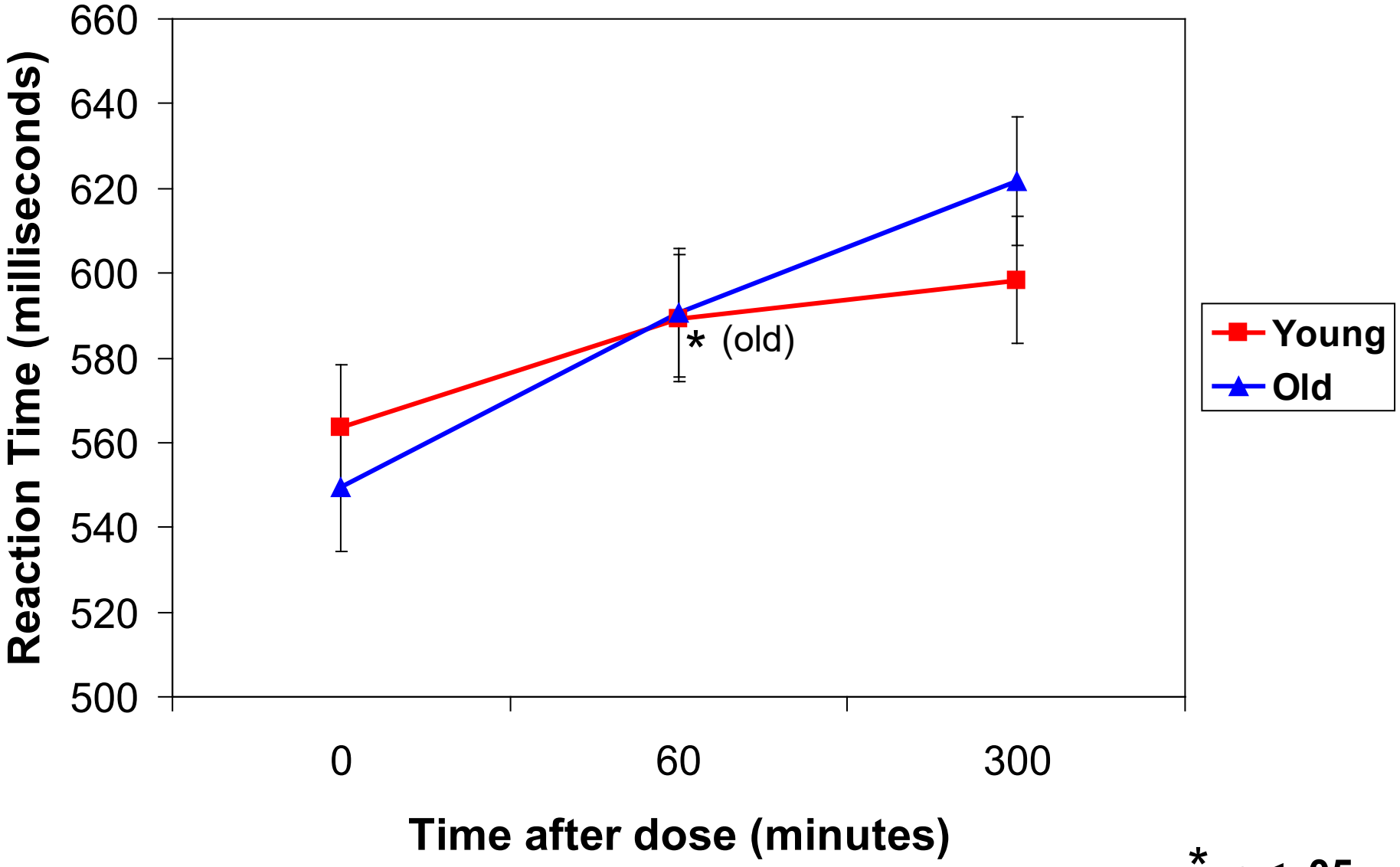
** $p < .01$

Simple Reaction Time



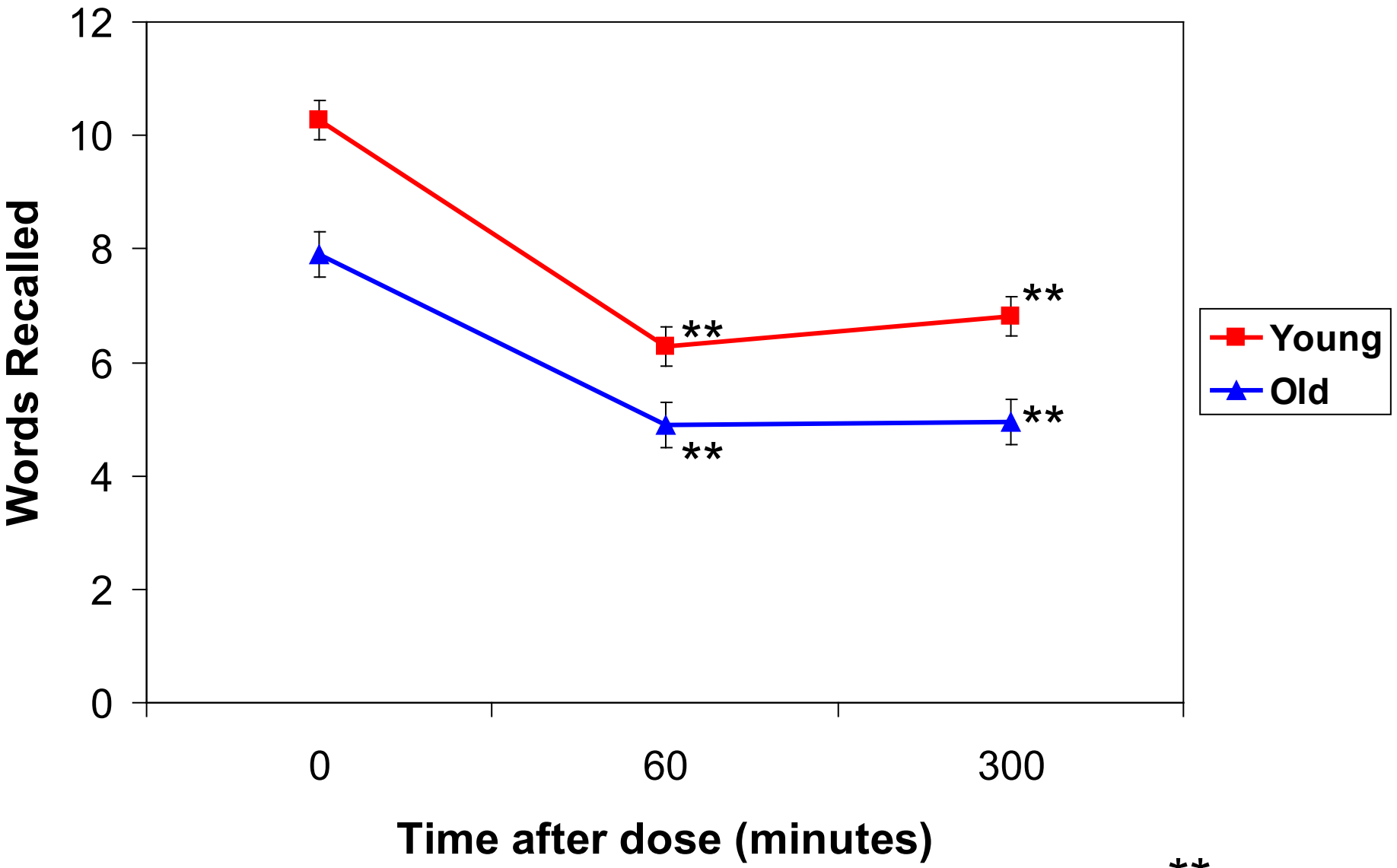
* $p < .05$ ** $p < .01$

Choice Reaction Time



* $p < .05$

HVLT - Verbal Memory: Delayed Recall

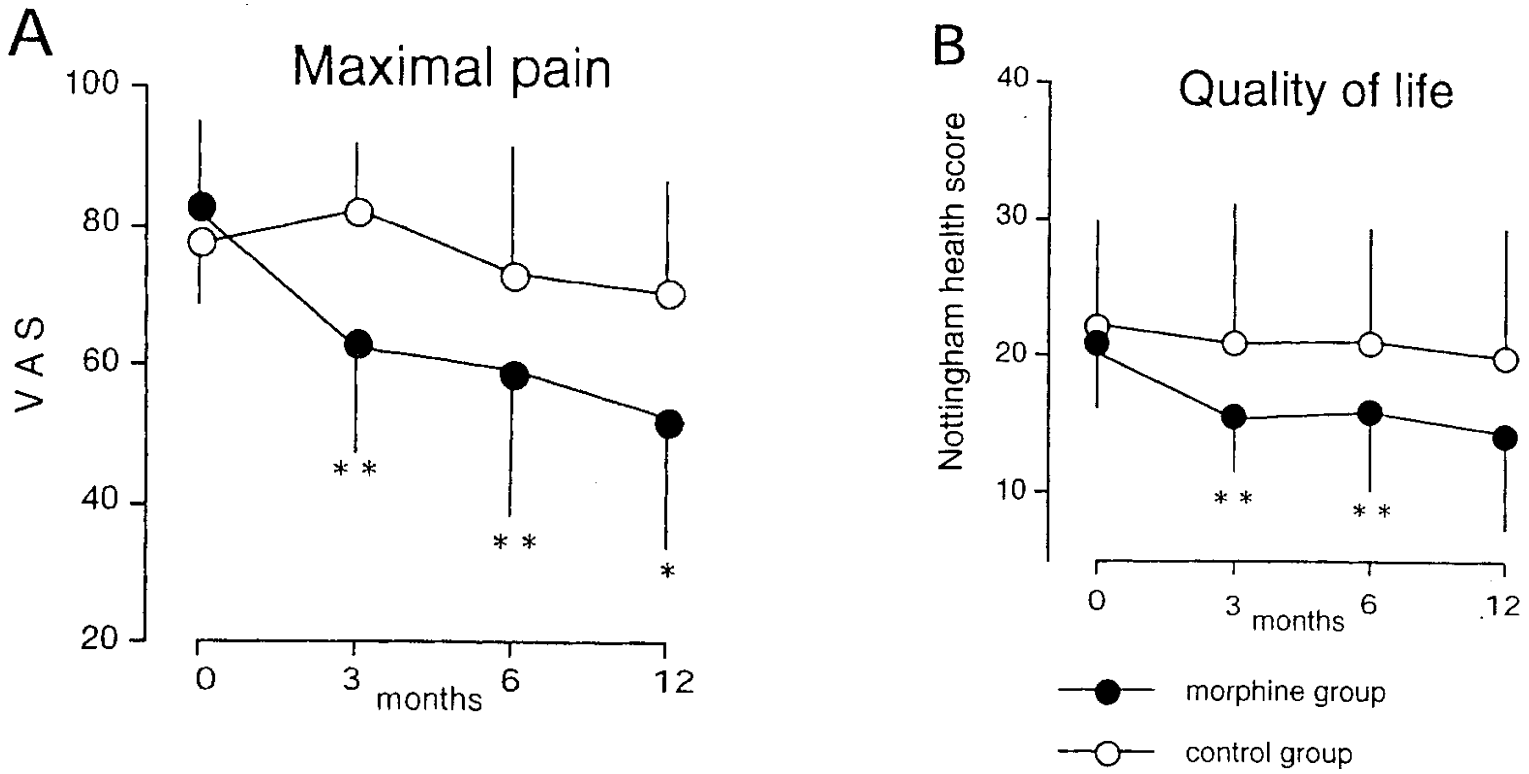


** $p < .01$

Sustained release opioid

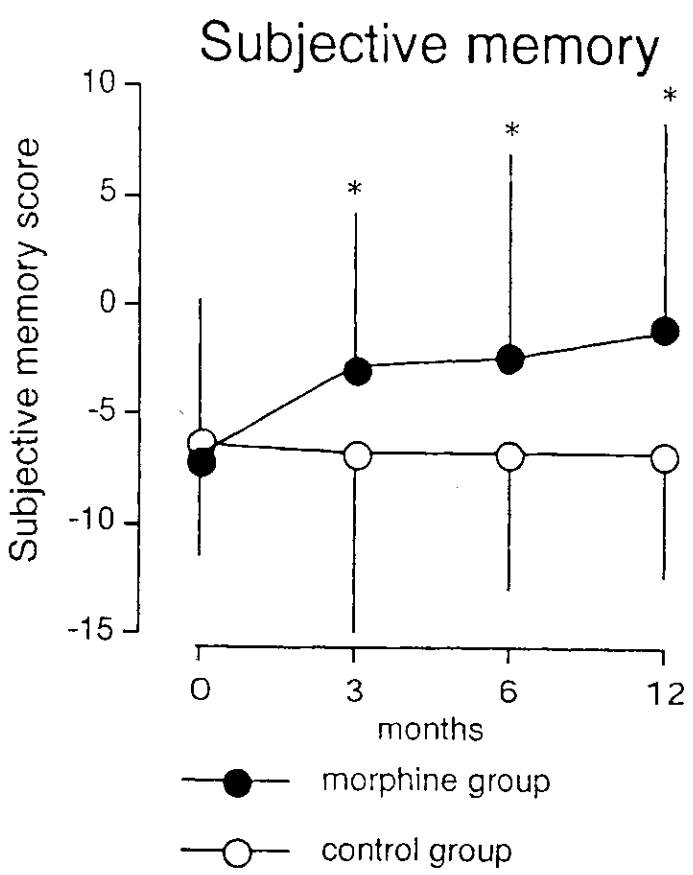
- Patients chronic non-malignant pain N=18
  - Oral sustained release morphine on a low dose and titrated up to efficacy or side effects and maintained on stable dose
- Neuropsychological, QOL & Mood assess. At baseline, 3, 6 and 12 months
  - Buschke, Stroop, TMT, WAIS, RT,

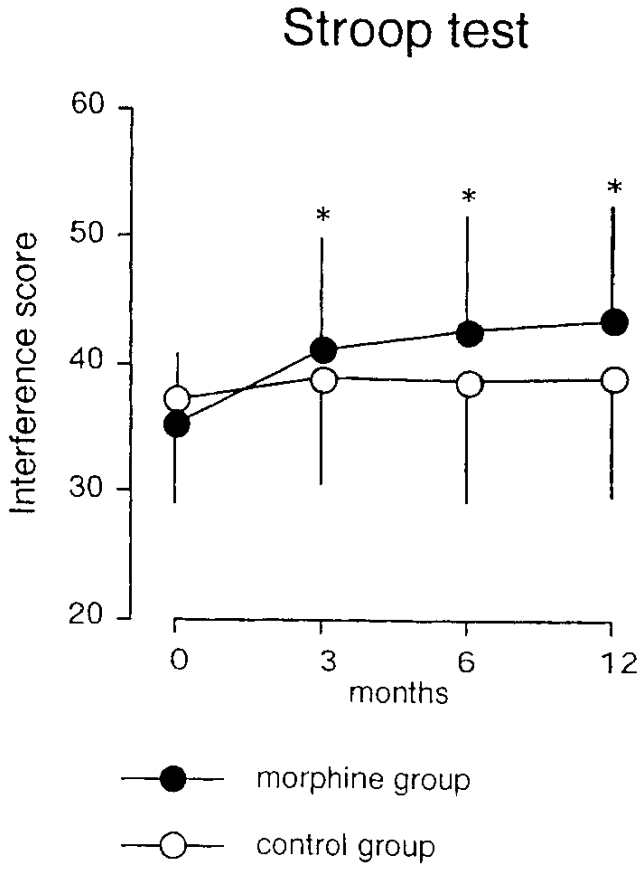
(Tassain et al., Pain, 2003)



- **Pain significantly decreased**
- **Overall Quality of life improved**

(Tassain et al., Pain, 2003)





Subjective memory rating improved
Objective performance improved: Stroop, Digit symbol

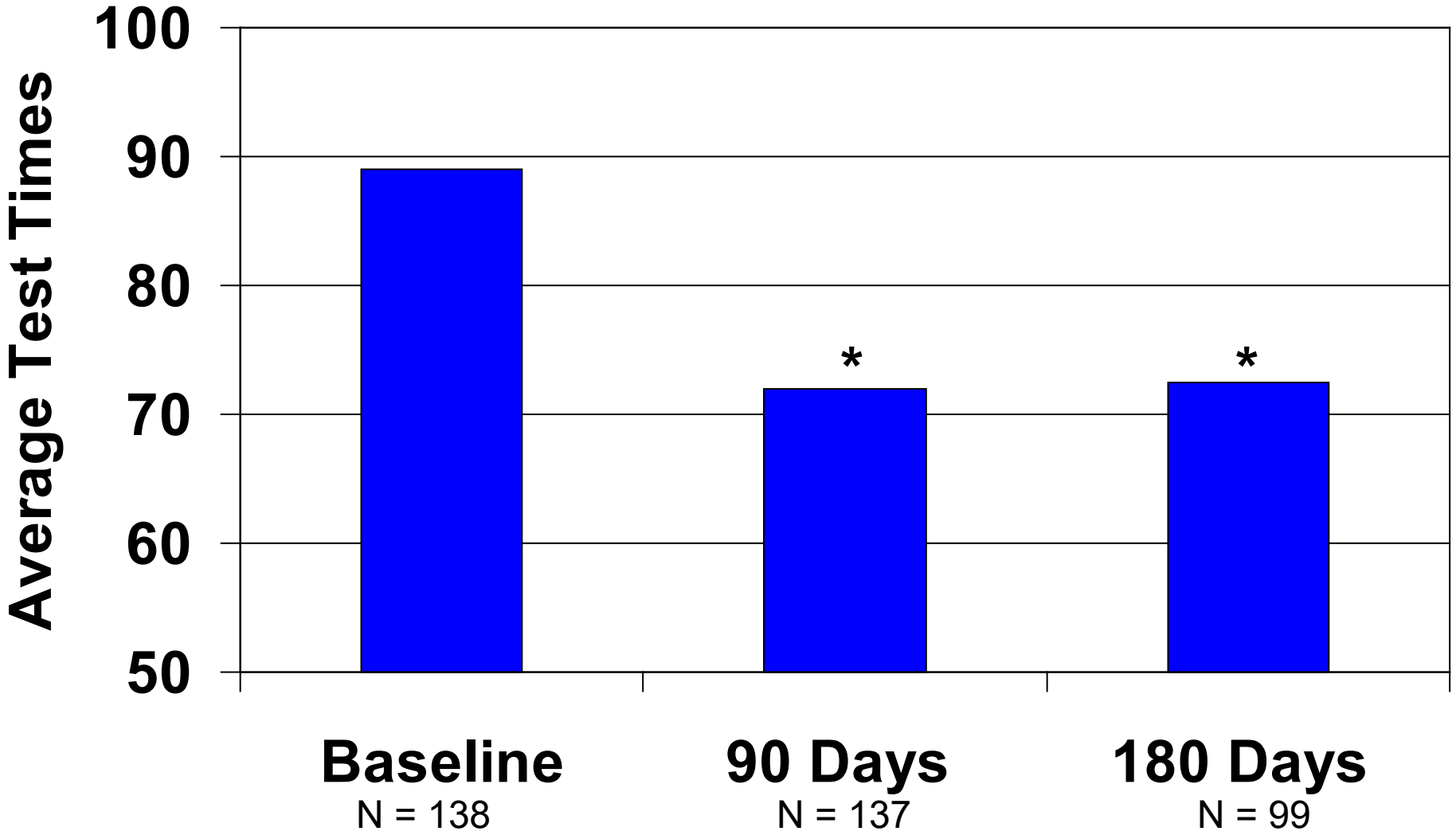
(Tassain et al., Pain, 2003)

Long Term Opioid Use

- N= 144 patients with chronic low back pain
- Mean age = 46 years
- Assesses prior to the start of oxycodone with acetometaphine vs transdermal fentanyl and again after 90 and 180 days
- Neuropsych. Tests and mood measures
  - DSST, Trail making test part B
  - BDI, SF-36

(Jamison, et al. JPSM, 2003)

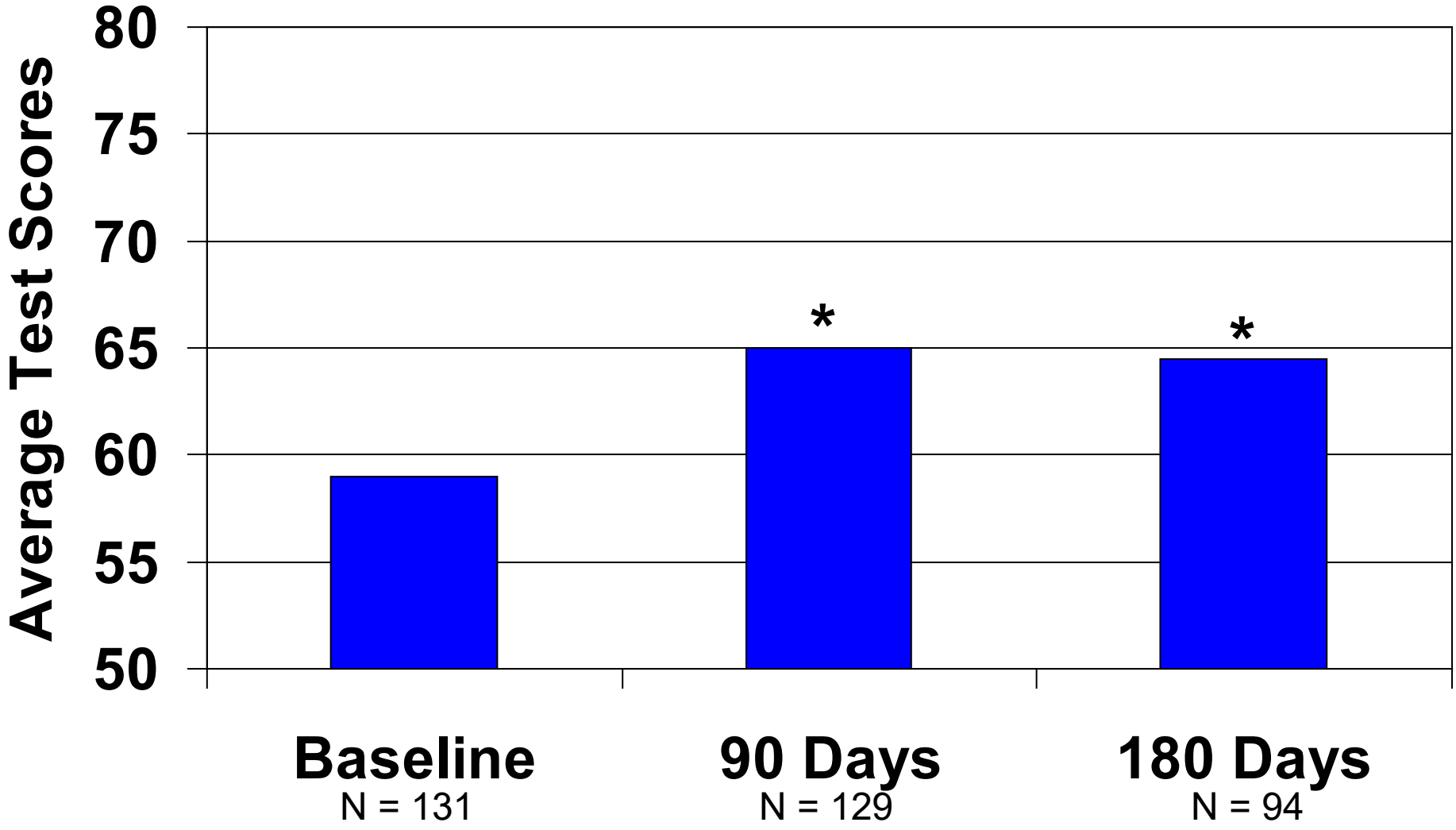
Mean Digit Symbol Substitution Test



(Jamison, et al. JPSM, 2003)

** P < 0.001, Change from baseline*

Mean Trail Making Test



(Jamison, et al. JPSM, 2003)

*** P < 0.001, Change from baseline**

Driving Assessment

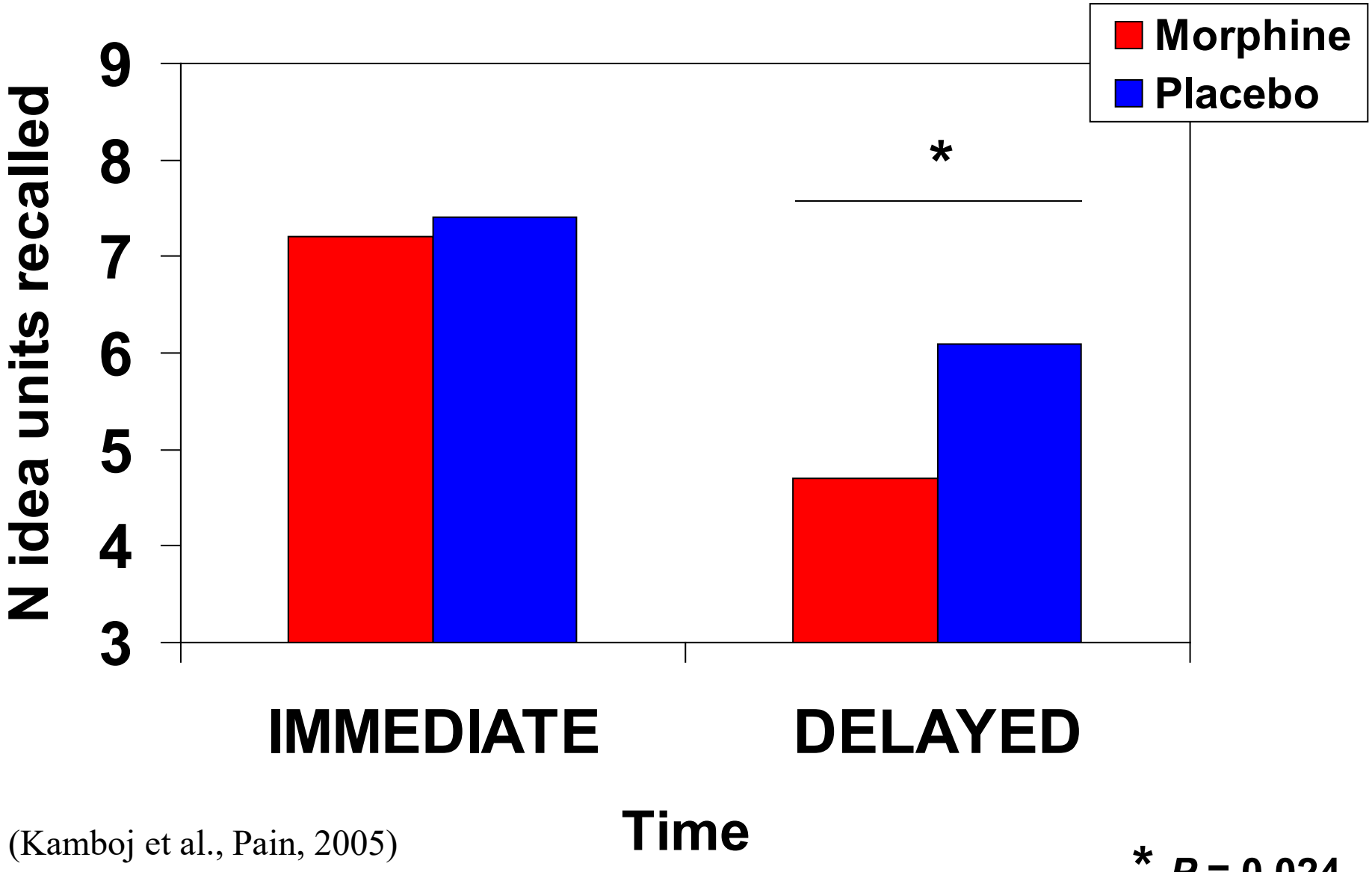
- Studies examining participants with chronic pain on stable doses of various opioids
- No sig. Difference between patients and controls
  - Gaertner et al, Acta Anesh. Scan. (2006) – CRO
  - Sabatowski et al. JPSM (2003) – transdermal fentanyl
  - Menefee et al., Pain, (2004) – transdermal fentanyl- & pts. Improved on visual motor tracking, visual memory and attention
- Sig. Decrements between pts. & controls
  - On two tests out of large battery- a test of continuous-monotonous attention (Schindler et al., Eur. Addit Res., 2004)
  - ? Used participants from drug addiction outpatient clinic on methadone or buprenorphine

Chronic Dosing + PRN use

- N= 14 patients receiving palliative care and taking a CR opioid
- Examined immediate verbal memory at baseline (RBANS) and larger battery of cognitive tests 45 minutes after taking IR opioid or placebo
  - Finger tapping, verbal fluency, elevator counting, digit span, immediate recall RBANS story 2 and delayed recall of 1 and 2, TEA

(Kamboj et al., Pain, 2005)

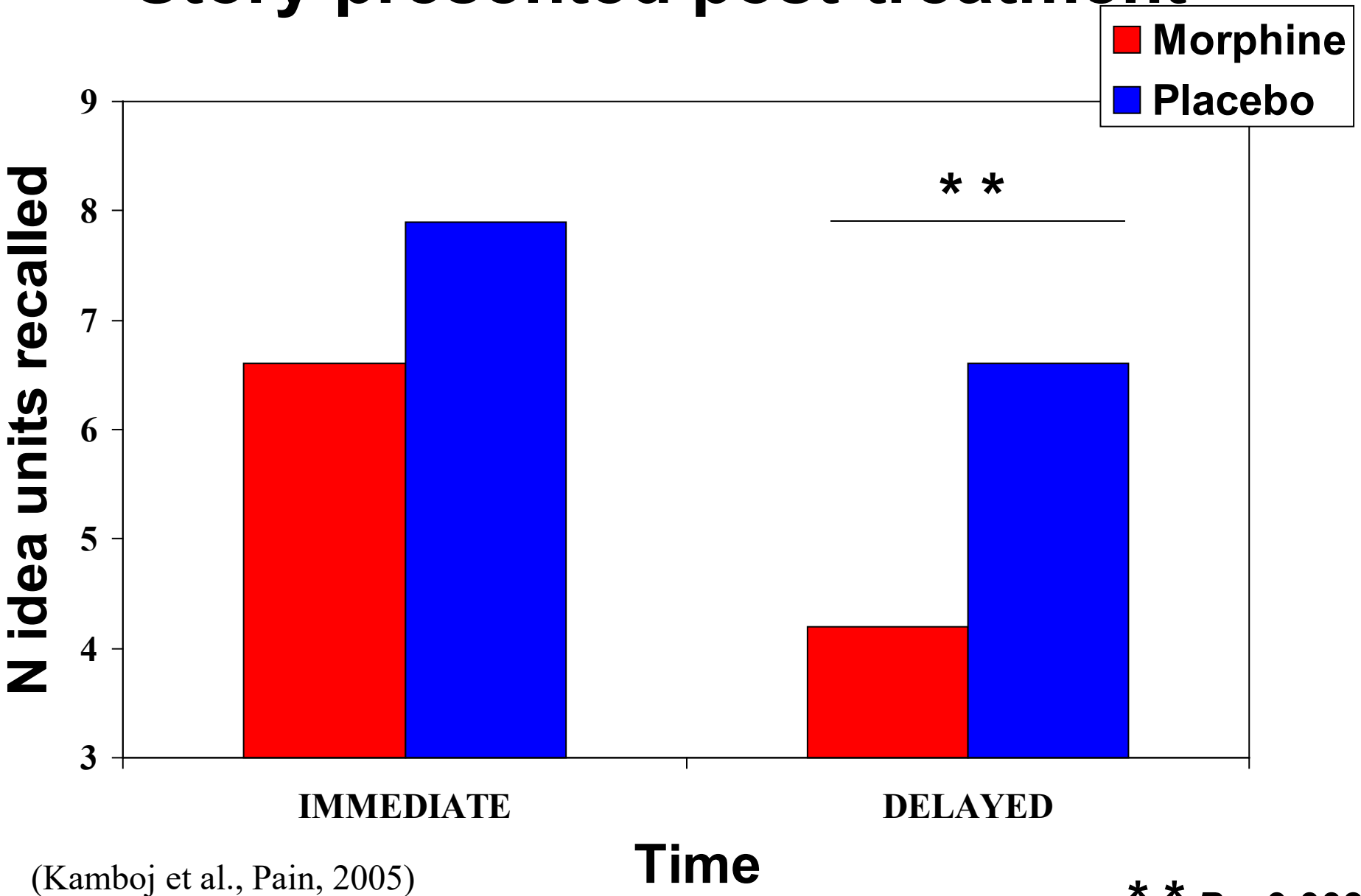
Story presented pre-treatment



(Kamboj et al., Pain, 2005)

* *P* = 0.024

Story presented post-treatment



(Kamboj et al., Pain, 2005)

* * *P* = 0.003

Results

- No other significant effects compared to placebo for:
  - Verbal fluency
  - Digit Span and Tests of Everyday Attention
  - Trail Making Test
  - Finger Tapping

(Kamboj et al., Pain, 2005)

Driving Assessment Caveats

- Other factors may interfere with optimum driving ability
  - Age
  - Risk taking/ impulsive/daring behavior
  - Previous driving record & defensive driving behaviors
  - Alcohol history
- Driving test may not be the best measure of driving performance

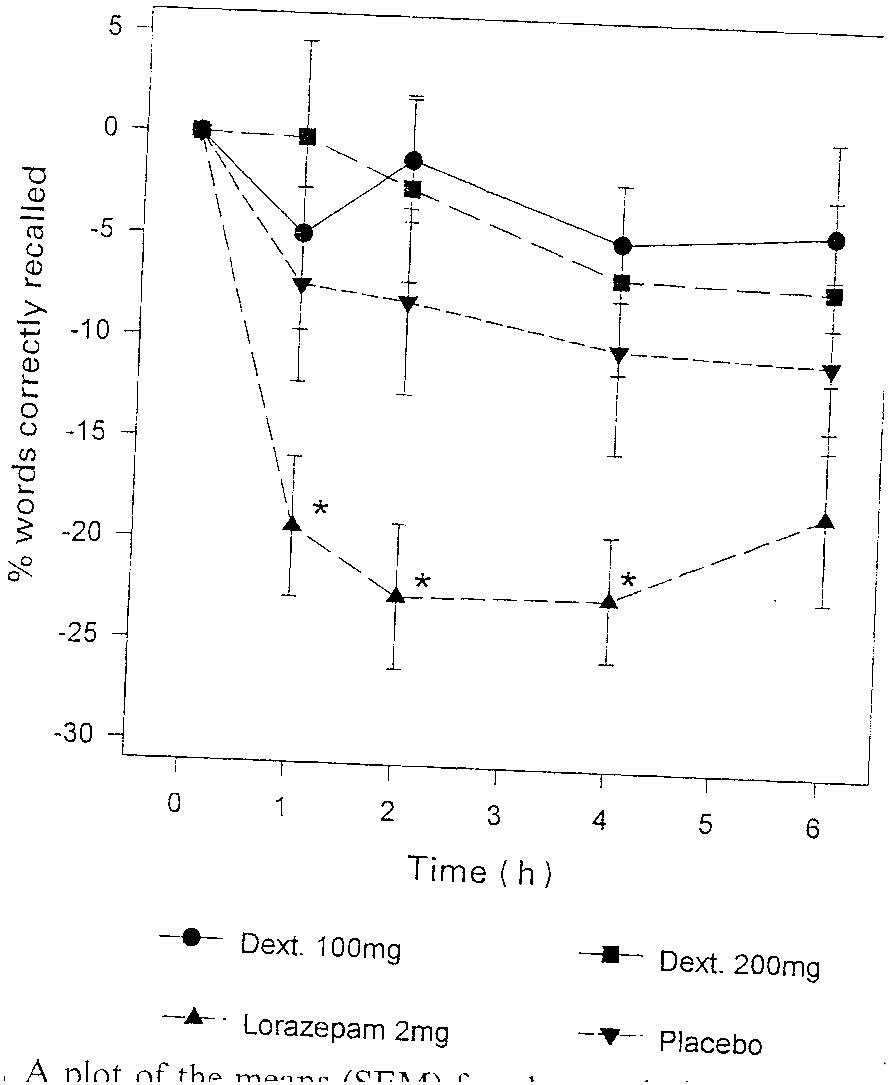
Additional Medication Cautions

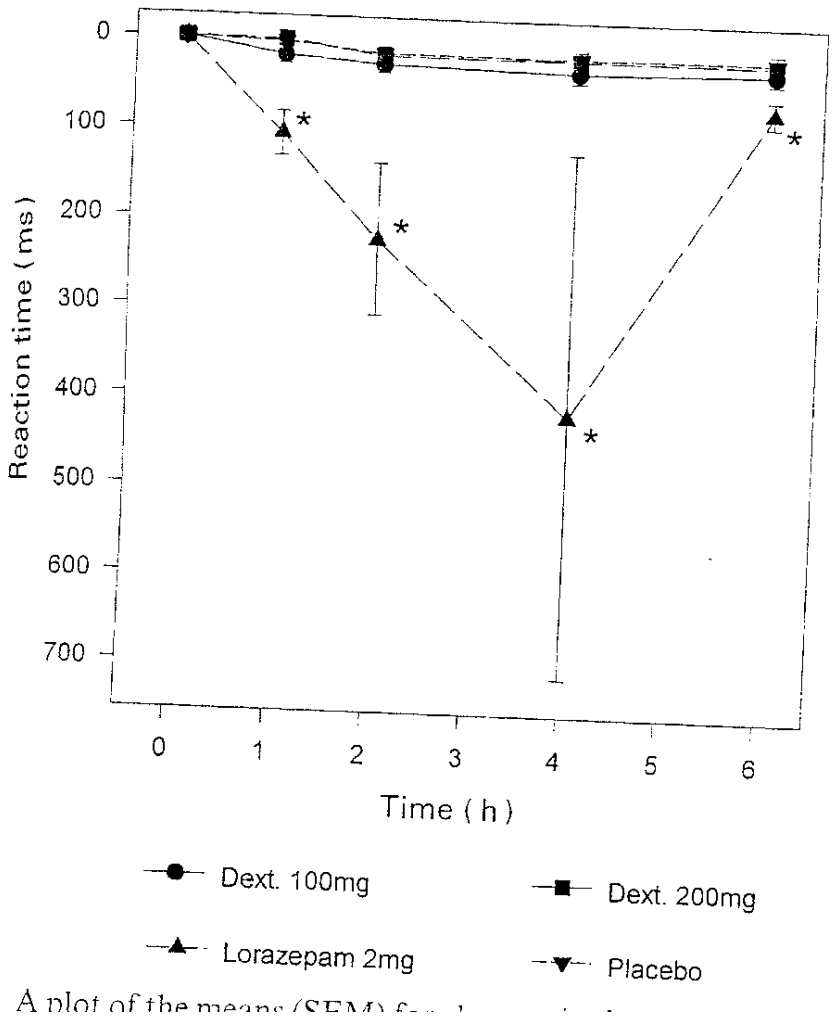
- Other medications and conditions can cause impairments in cognition and driving abilities
  - Sleep apnea
  - Vascular conditions and heart medications
  - Sleep deprivation
  - Other medications and medical conditions- cancer, benzodiazepines, asthma- allergy medications

Opioids vs Benzodiazepines

- Four way cross over experiment
  - 100mg, 200mg dextropropoxyphene
  - 2mg lorazepam
  - Placebo
- Battery of cognitive tests –computerized CDR
  - Word recall, RT, picture recognition, scanning, vigilence
- Testing at baseline, 1, 2, 4, and 6 hours post drug

Wesness et al., Eur. J. C. Pharm. (1995)





Lorazepam –significant decline in word recall and reaction time

Wesness et al., Eur. J. C. Pharm. (1995)

Summary & Recommendations

- Pain and chronic pain can have adverse effects on cognition
  - May be modulated by mood, health & motivation
- Pain medications may have adverse effects on cognition
  - Immediate release, IV, dose escalation or PRN immediate release on top of SR, modulated by other factors such as age, health status

Summary and Recommendations

- Individuals who are on stable doses of sustained release opioids
  - Demonstrate minimal or no adverse effects of medication
  - May be considered safe to drive- with caveats
- Other medications and medical conditions and mood states may have a greater impact on cognitive functioning
- There can be a disconnect or lack of association between subjective sense of cognitive abilities and actual performance

Summary and Recommendations

- Be cautious about performing tasks during peak drug effects when increasing opioid dose or taking a prn dose for breakthrough pain
- Rely upon memory aids
- Wait until peak drug levels have started to decline for cognitively demanding tasks