

# New Intra-articular Therapy for Osteoarthritis

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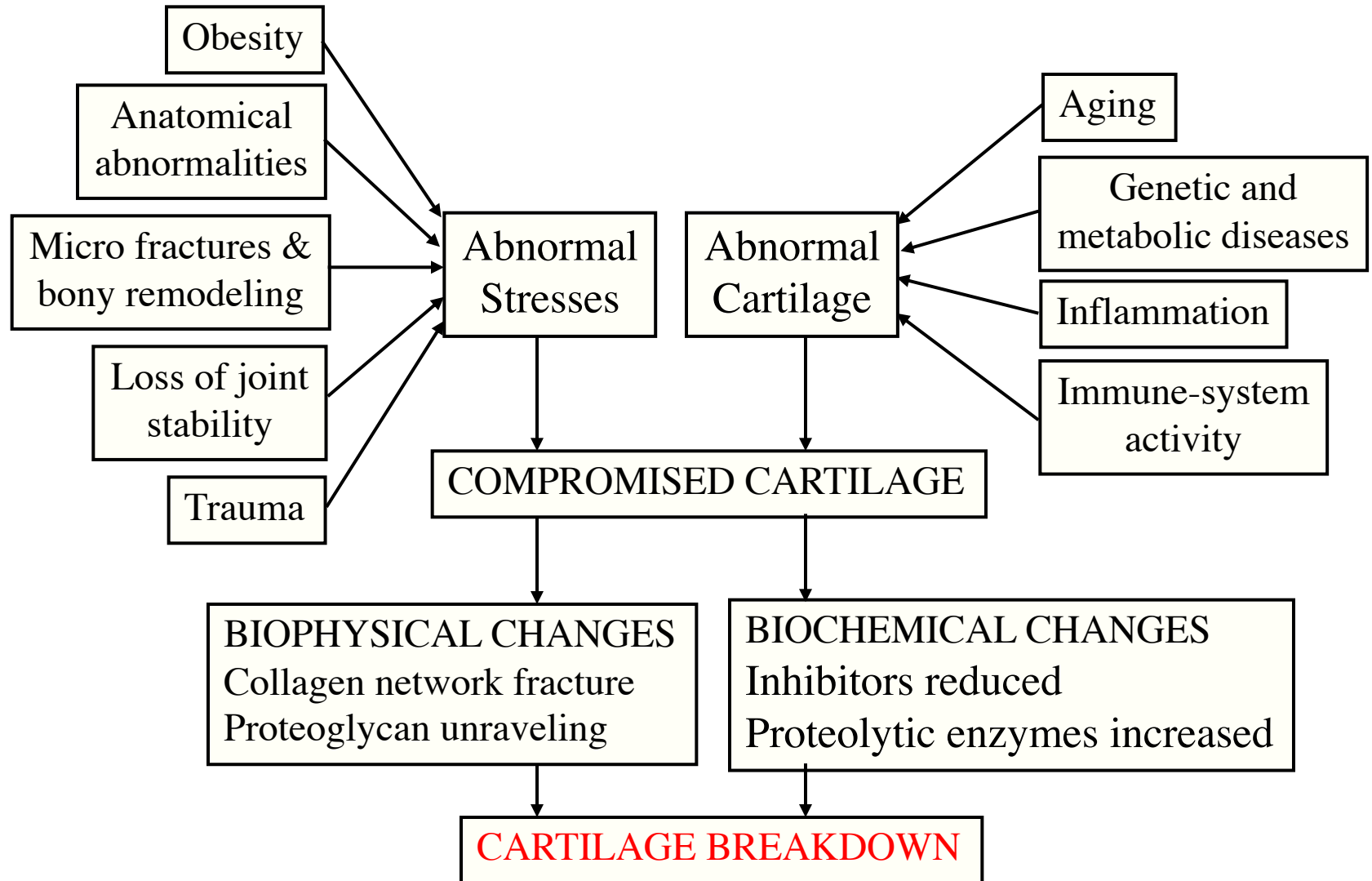
LSU Medical School

Shreveport, Louisiana

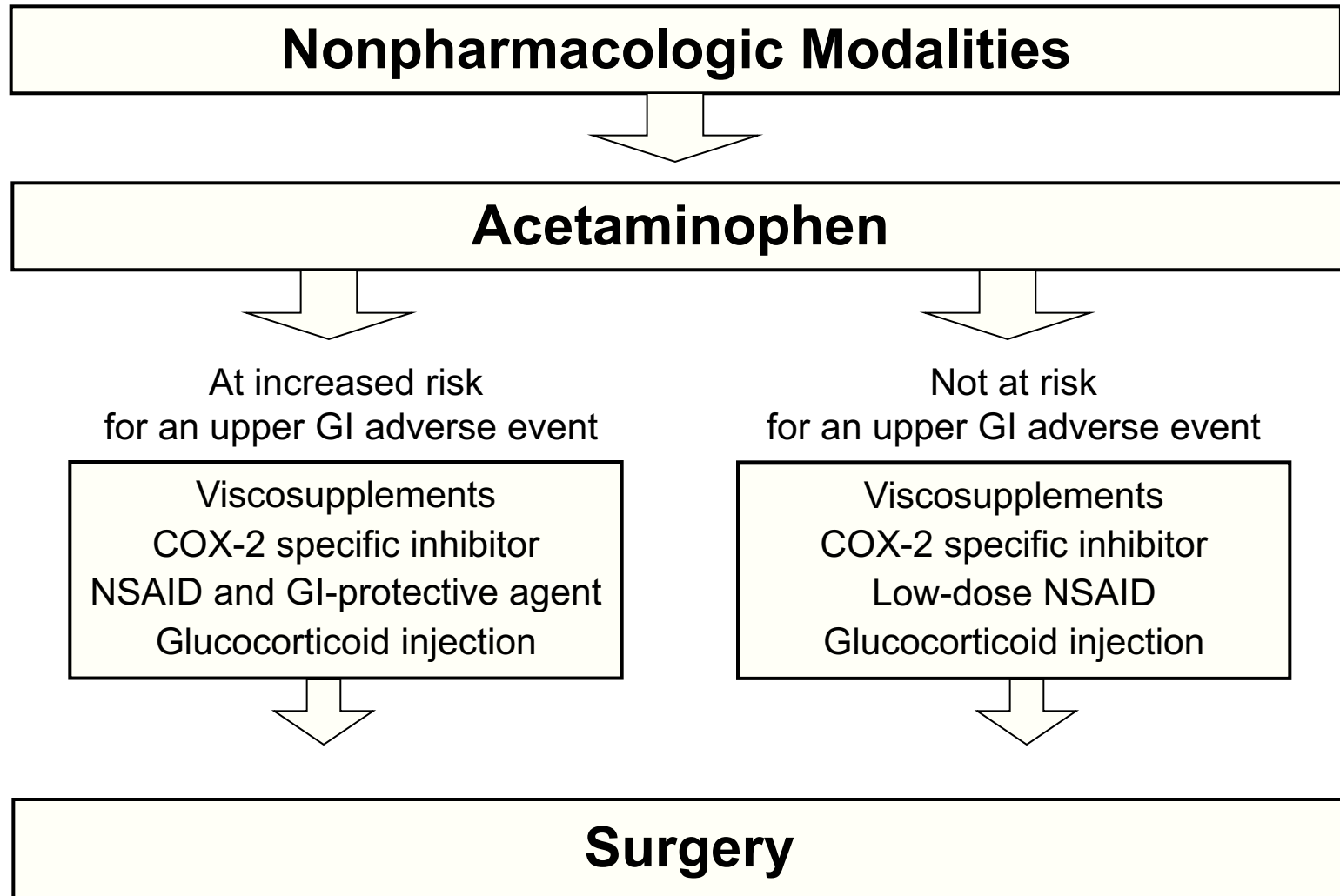
# Summary

- Background
- *In vitro* study
- Animal study
- Clinical studies
- Future plans

# Factors Involved in Osteoarthritis



# American College of Rheumatology 2000 Guidelines



# Advantages of Local Treatment

- OA is a local disease
- Local therapy avoids systemic adverse events (COX II side-effects)
- Lower doses of therapeutic agents

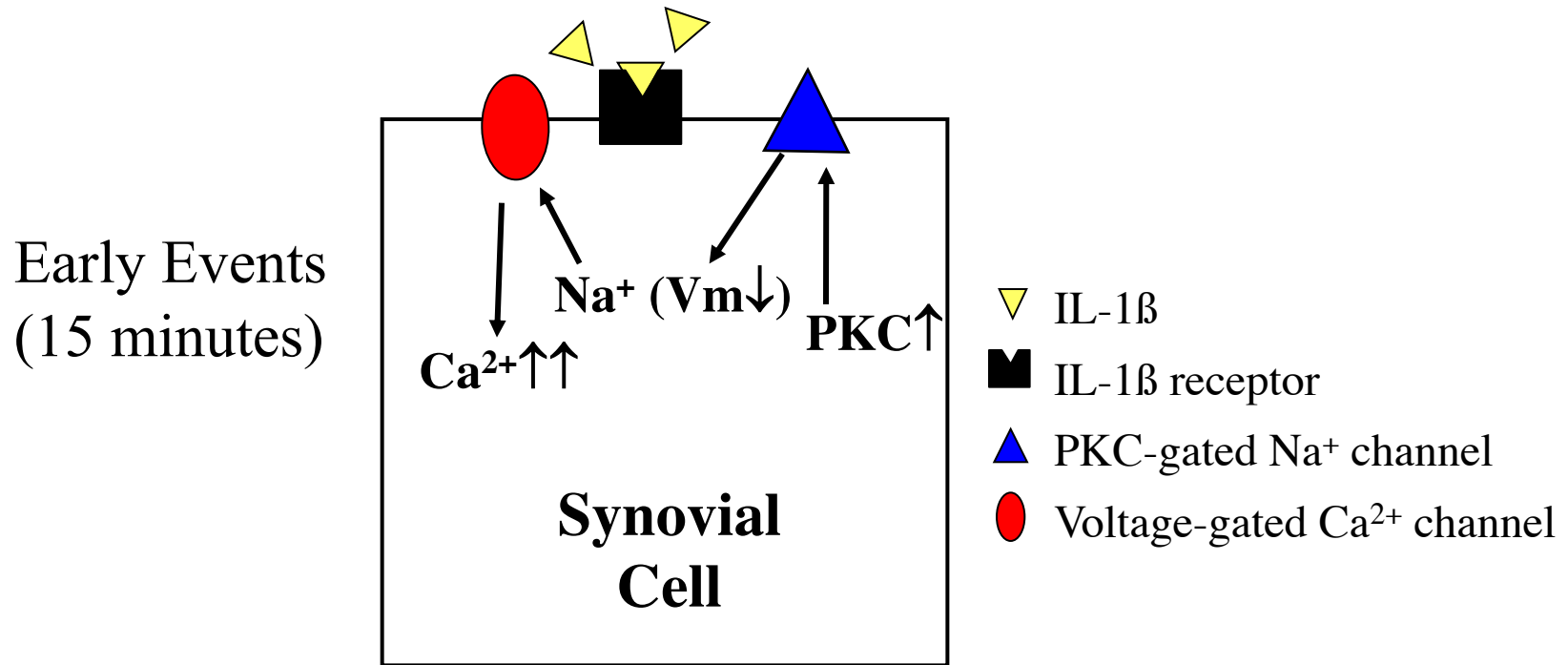
# Osteoarthritis Local Therapies

- Intra-articular steroids
- Hyaluronans
- Transdermal non-steroidal agents
- New agents?

# Background of Laboratory Research

# Important Discovery

## Signal Transduction in Synovial Cells



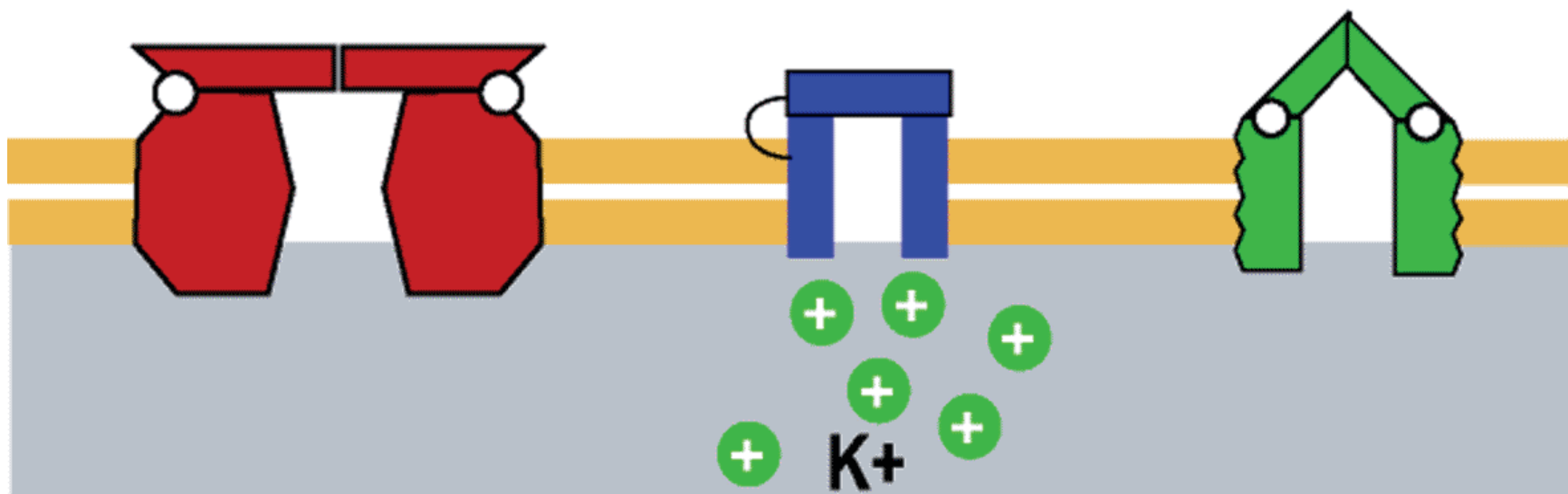
Late Events  
(2-48 hrs)

**MMPs  $\rightarrow$  OA**

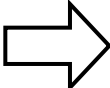


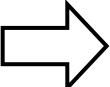
Na<sup>+</sup>

Ca<sup>++</sup>



# Proposed Membrane-Channel Research

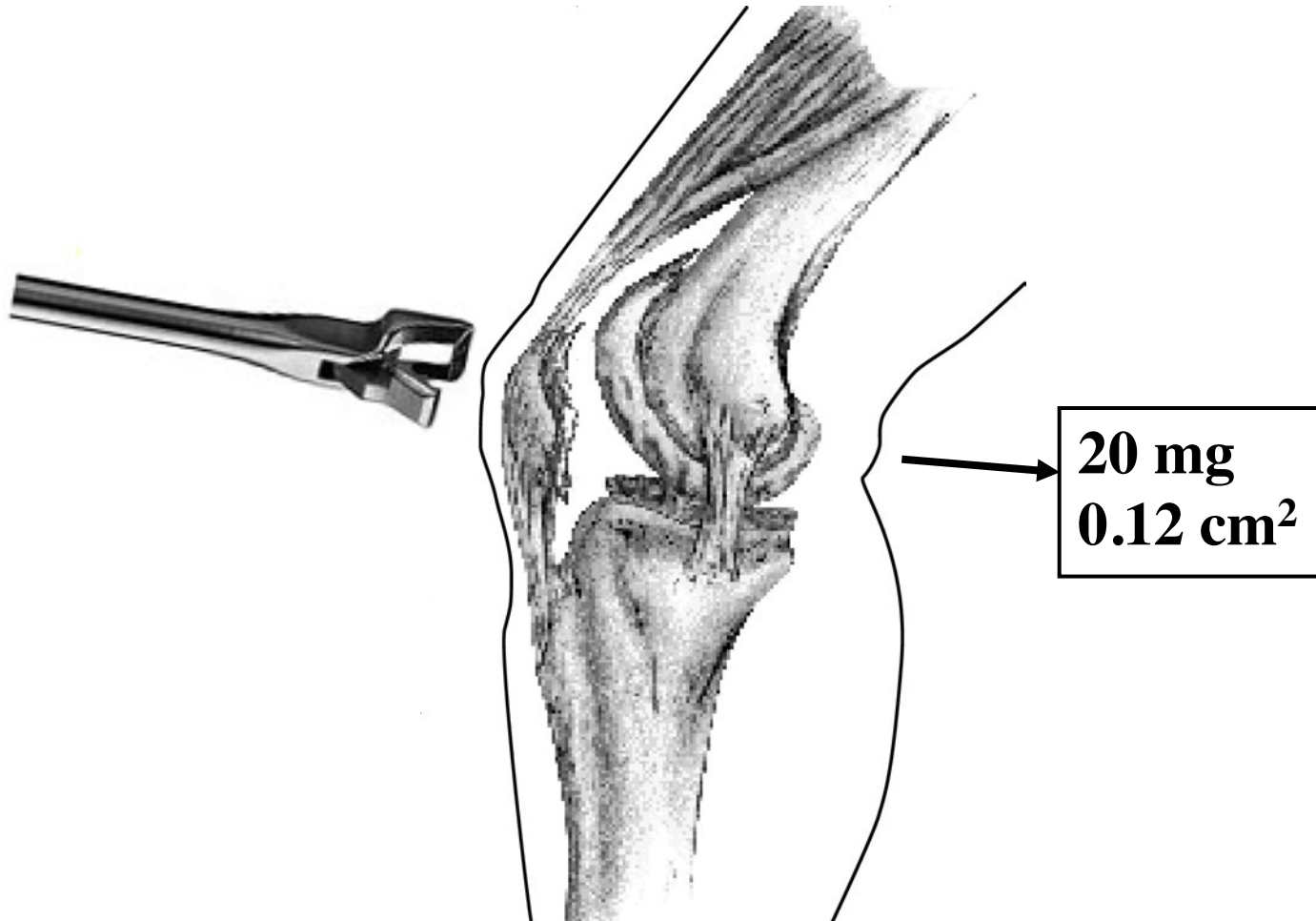
Basic Idea  Pathological changes in specific ion channels mediate progression of OA

- Proposal 
- 1) Identify the channels functionally by comparing OA and normal synovial cells
  - 2) Design chemical agents to block the altered channels

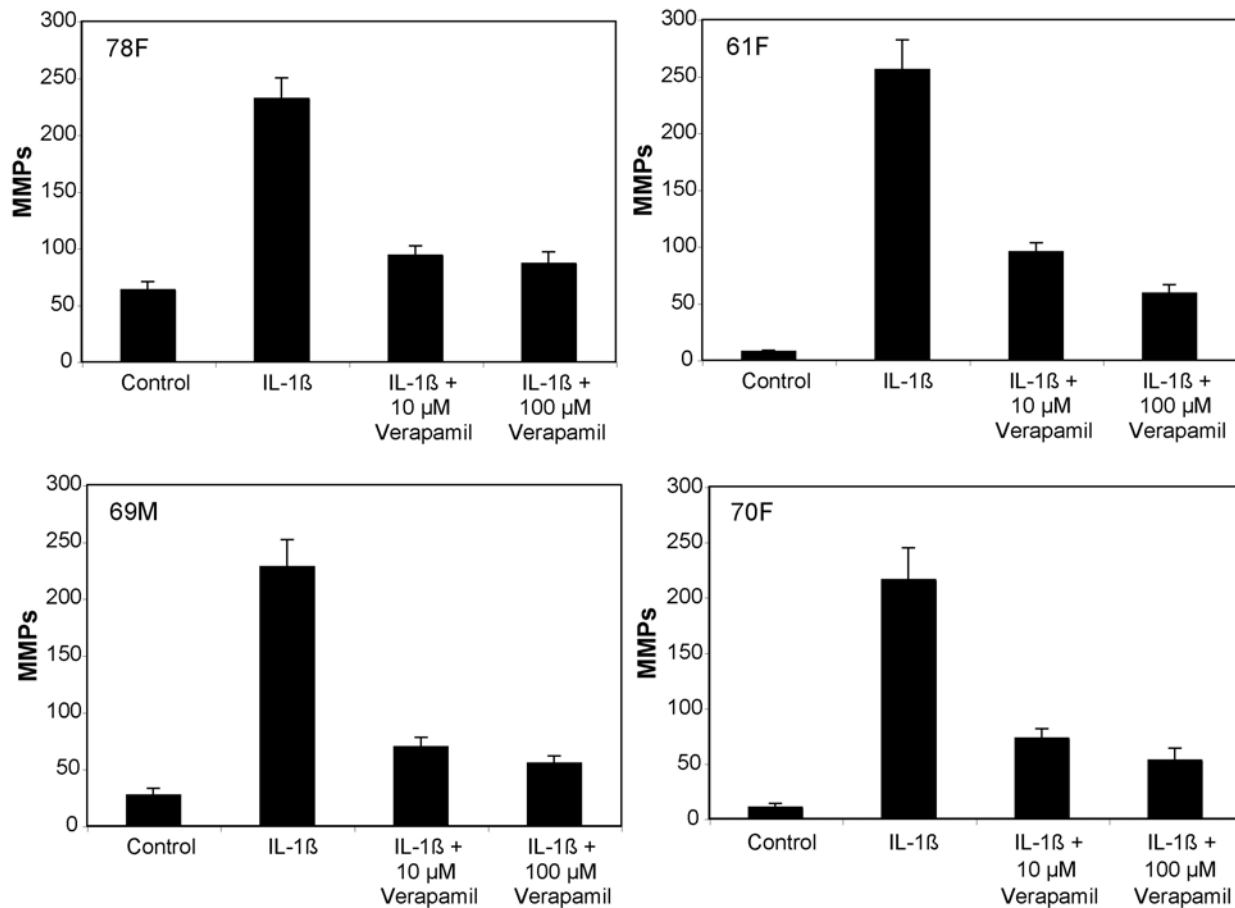
# Plan

Inject blockers that are already on the market for heart problems

# Surgical Biopsy Procedure



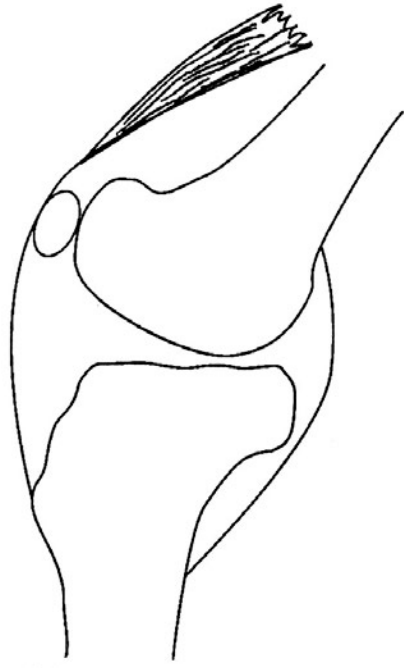
# *In Vitro* Study: Effect of Calcium-Channel Blocker Verapamil on MMP Production



# Animal Safety Study: Mouse Verapamil Study

Animals:	BALB/c ♂, 6 months old
Dose:	0.4-2.5 $\mu\text{g}/10 \mu\text{L}$ ( $\leq 100 \mu\text{M}$ )
Injection Site:	Knee (intra-articular)
Recovery Times:	4 hrs, 24 hrs, 4 days
Endpoint:	Inflammation

# Histological Evaluation



- Mid-sagittal plane used for evaluation
- Inflammation scale 0-3
- Scoring by blinded observer (pathologist)

# Mouse Study Results

## Results at Specific Time Points

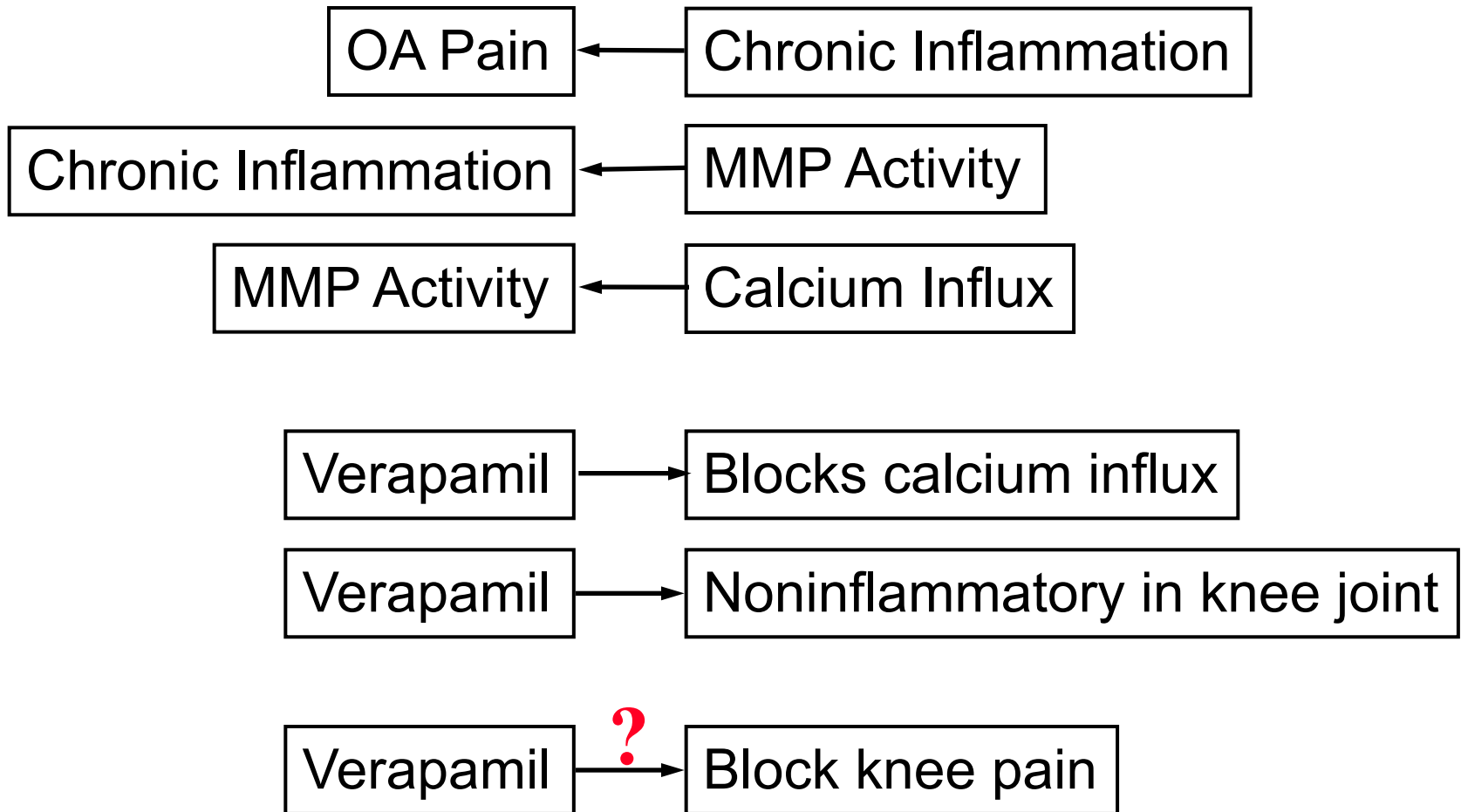
	<u>4 Hours</u>		<u>1 Day</u>		<u>4-5 Days</u>	
Histological Score	<u>0-1</u>	<u>2-3</u>	<u>0-1</u>	<u>2-3</u>	<u>0-1</u>	<u>2-3</u>
Verapamil	5	1	5	1	3	1
Control	1	3	1	3	3	1

## Overall Result

Histological Score	<u>0-1</u>	<u>2-3</u>	OR = 6.1 P < 0.05
Verapamil	13	3	
Control	5	7	



# Overall View

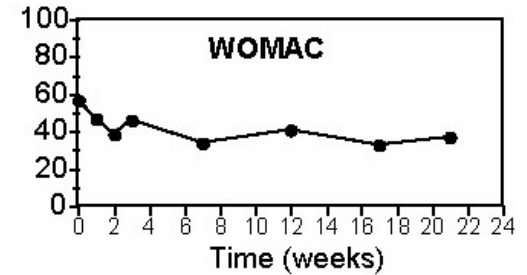
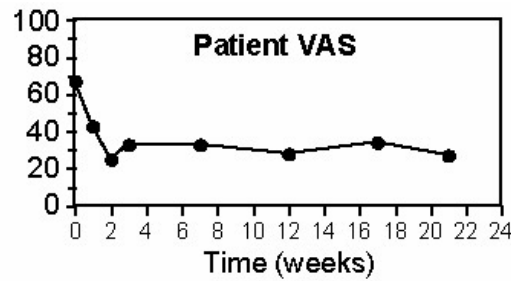
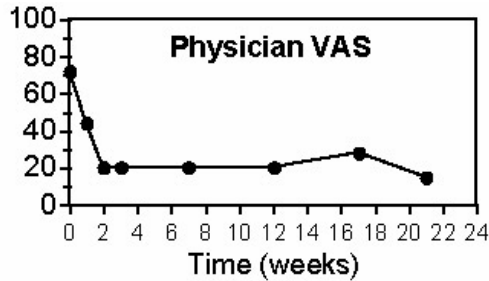


# Open Study Evaluating Verapamil in Osteoarthritis of the Knee

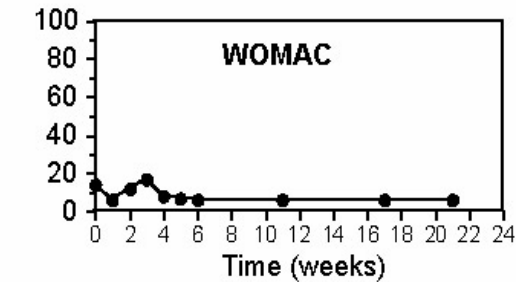
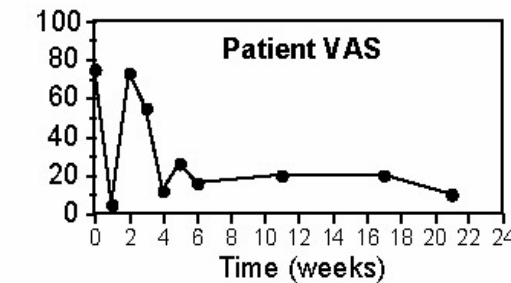
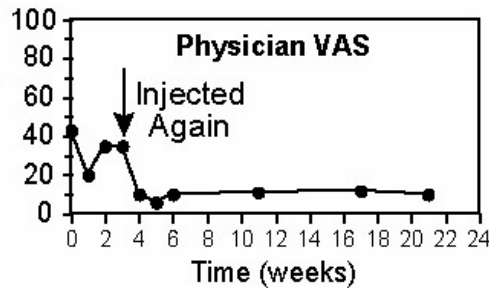
IRB ..... LSUHSC-S  
Study Design ..... Open study (no contemporaneous control)  
Principal Investigator ..... David Waddell, M.D.  
Other Investigators ..... None  
Dose ..... 0.2 mg & 0.5 mg  
Inclusion Criteria ..... Kellgren-Lawrence grade 4  
Study Hypothesis ..... Symptomatic treatment of OA pain  
Study Endpoints ..... WOMAC, Physician VAS, Patient VAS  
Follow-up Schedule ..... 1, 2, 3, 4, 5, 16, 20 weeks

# Verapamil Study No. 1 (0.2 mg)

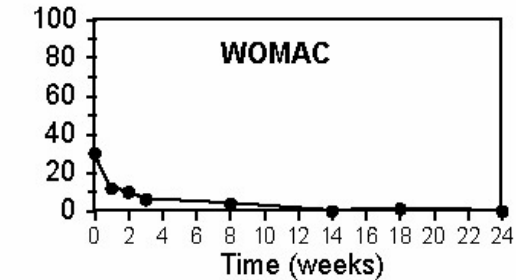
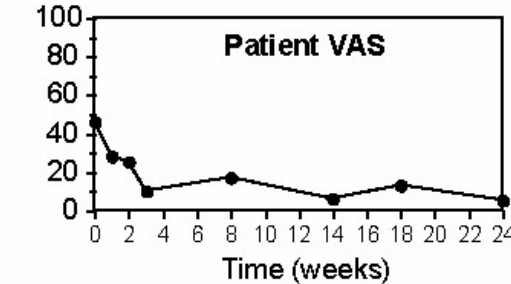
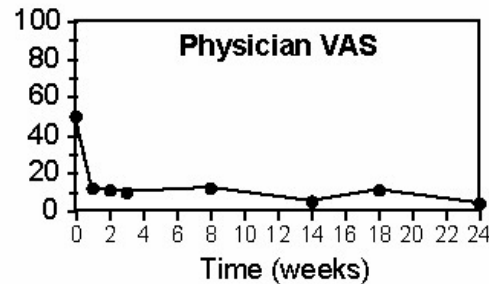
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57F  
(1-1)



Pt. No. 2  
41M  
(1-2)

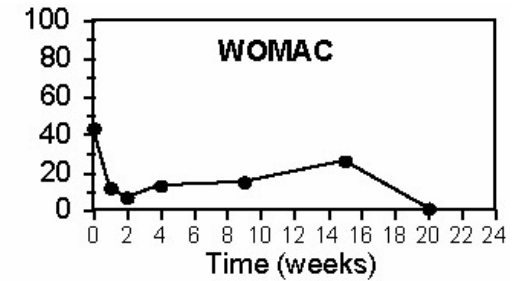
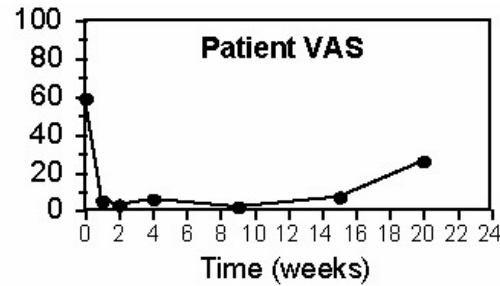
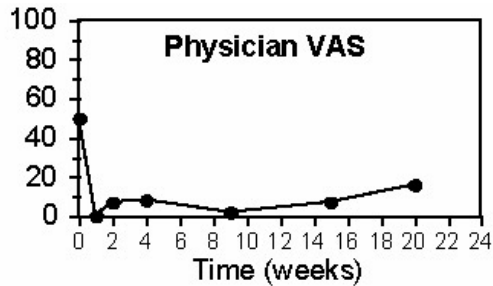


Pt. No. 3  
73M  
(1-3)

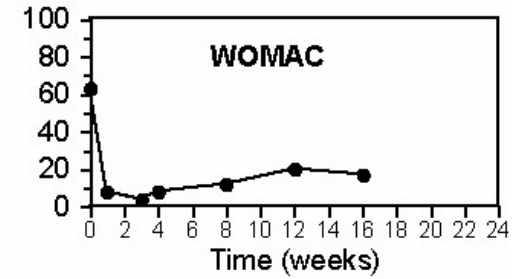
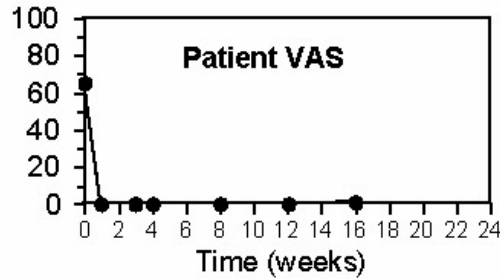
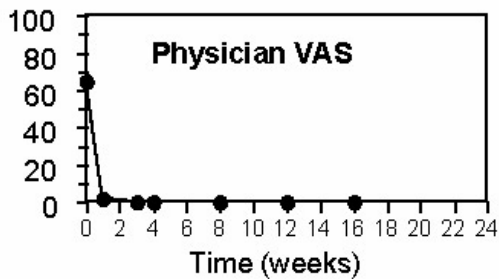


# Verapamil Study No. 1 (0.2 mg)

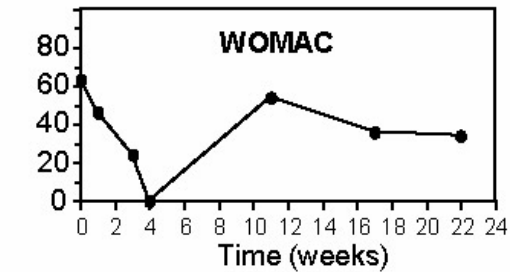
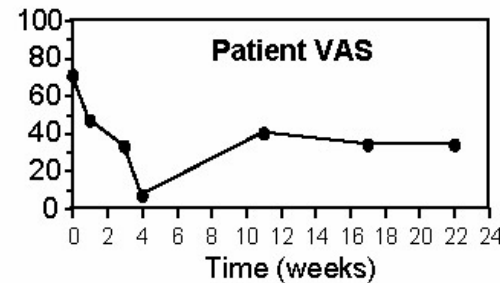
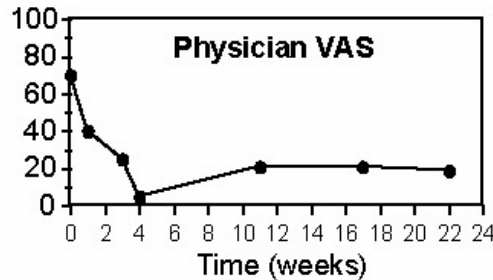
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(1-4)



Pt. No. 5  
63M  
(1-5)

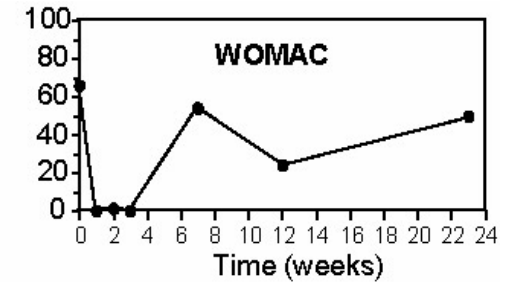
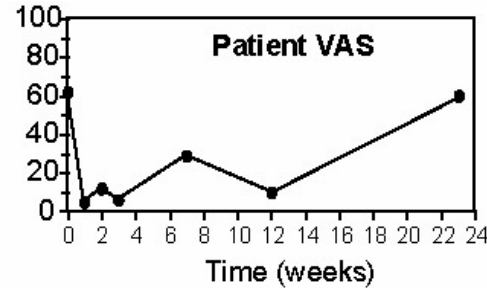
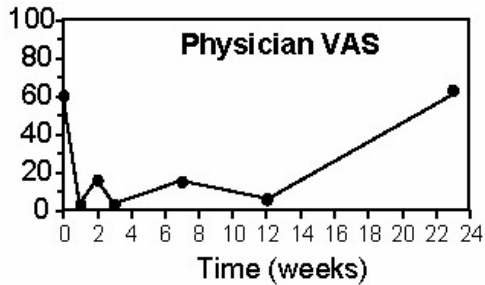


Pt. No. 6  
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(1-6)

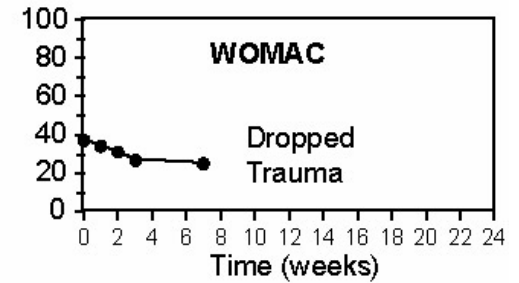
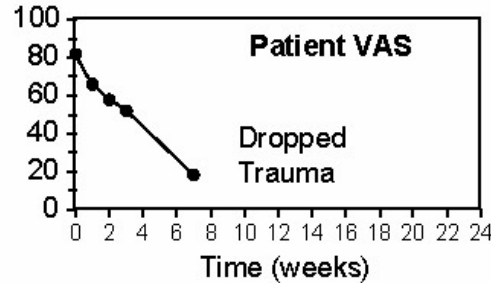
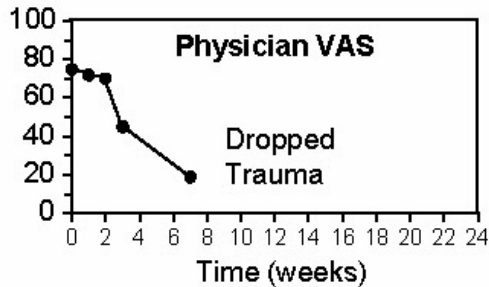


# Verapamil Study No. 1 (0.2 mg)

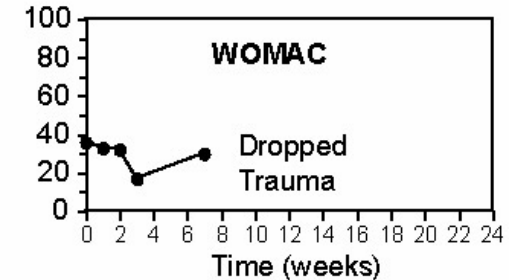
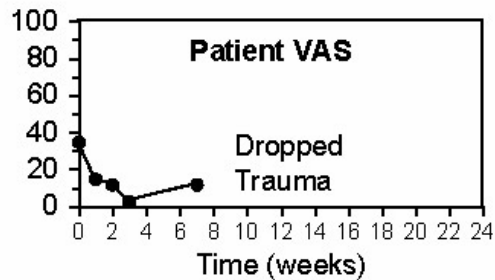
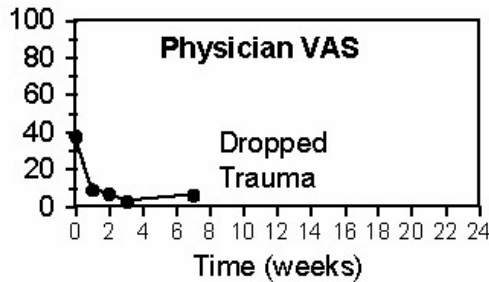
Pt. No. 7  
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(1-7)



Pt. No. 8  
54M  
(1-8)

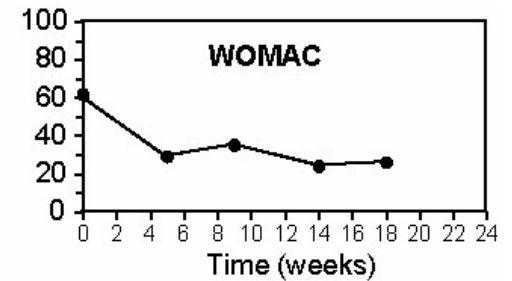
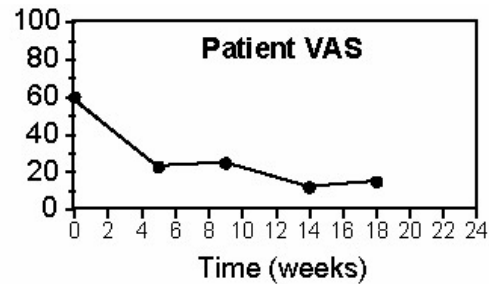
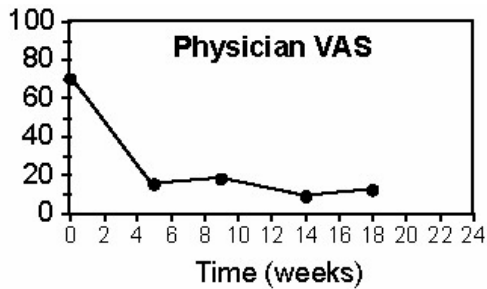


Pt. No. 9  
41F  
(1-9)

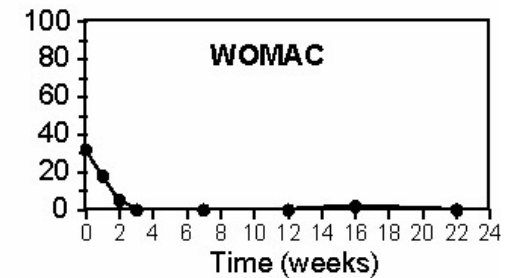
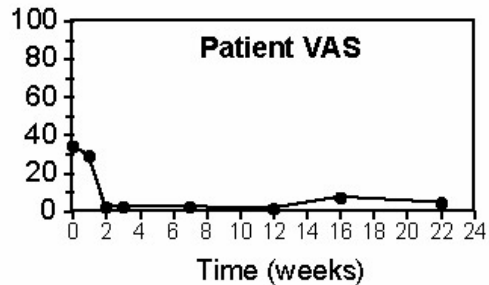
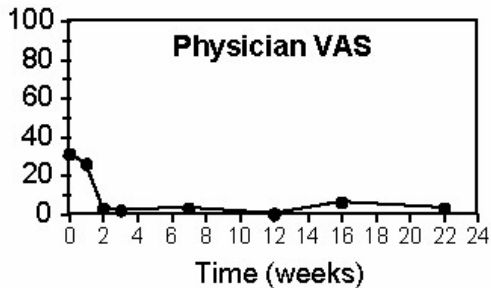


# Verapamil Study No. 1 (0.2 mg)

Pt. No. 10  
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(1-10)

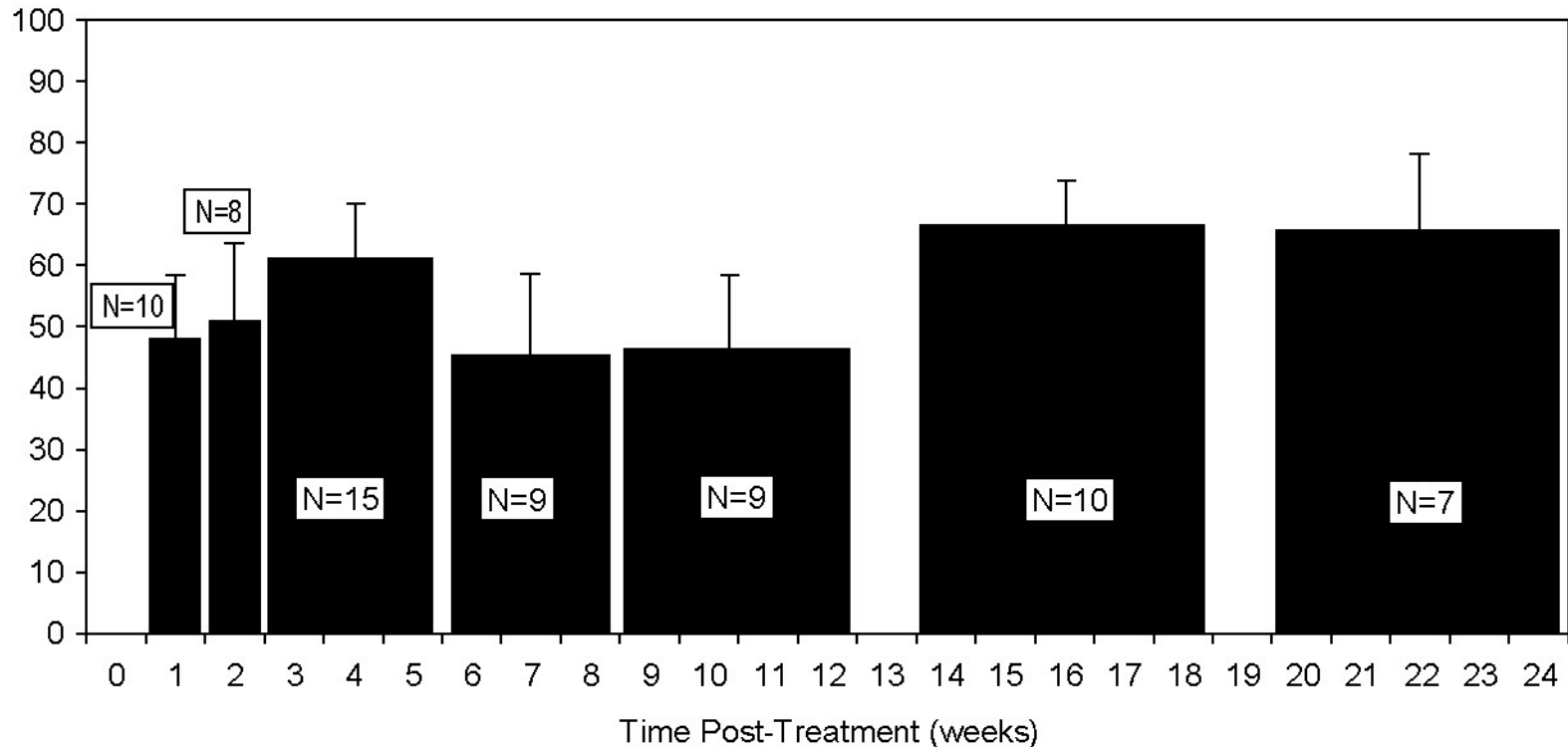


Pt. No. 11  
55M  
(1-11)



# Verapamil Study No. 1 (0.2 mg)

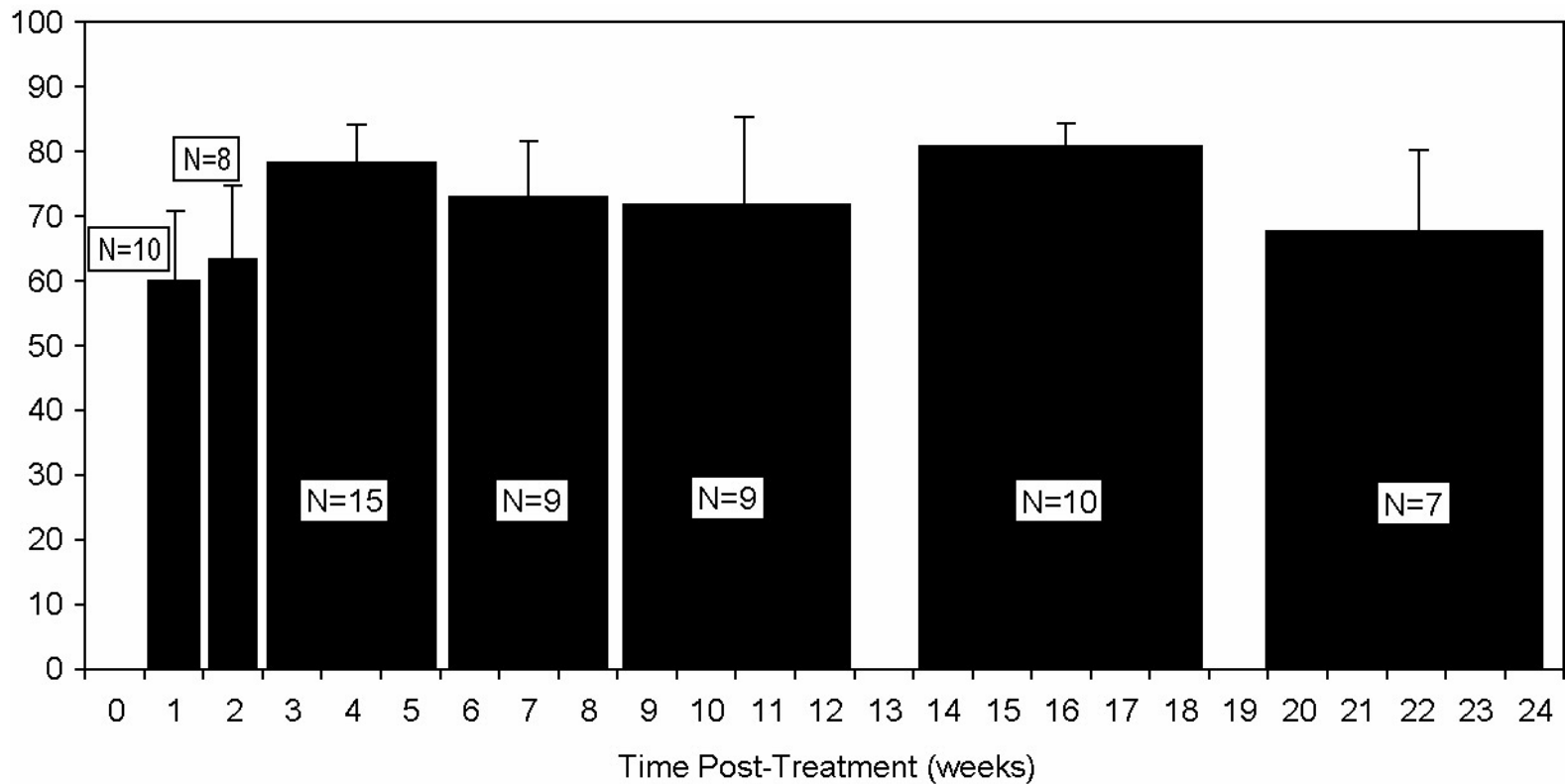
## % Decrease in WOMAC



$$\% \text{Decrease} = \frac{\text{score at } t=0 - \text{score at } t}{\text{score at } t=0} \times 100$$

# Verapamil Study No. 1 (0.2 mg)

## % Decrease in Physician VAS

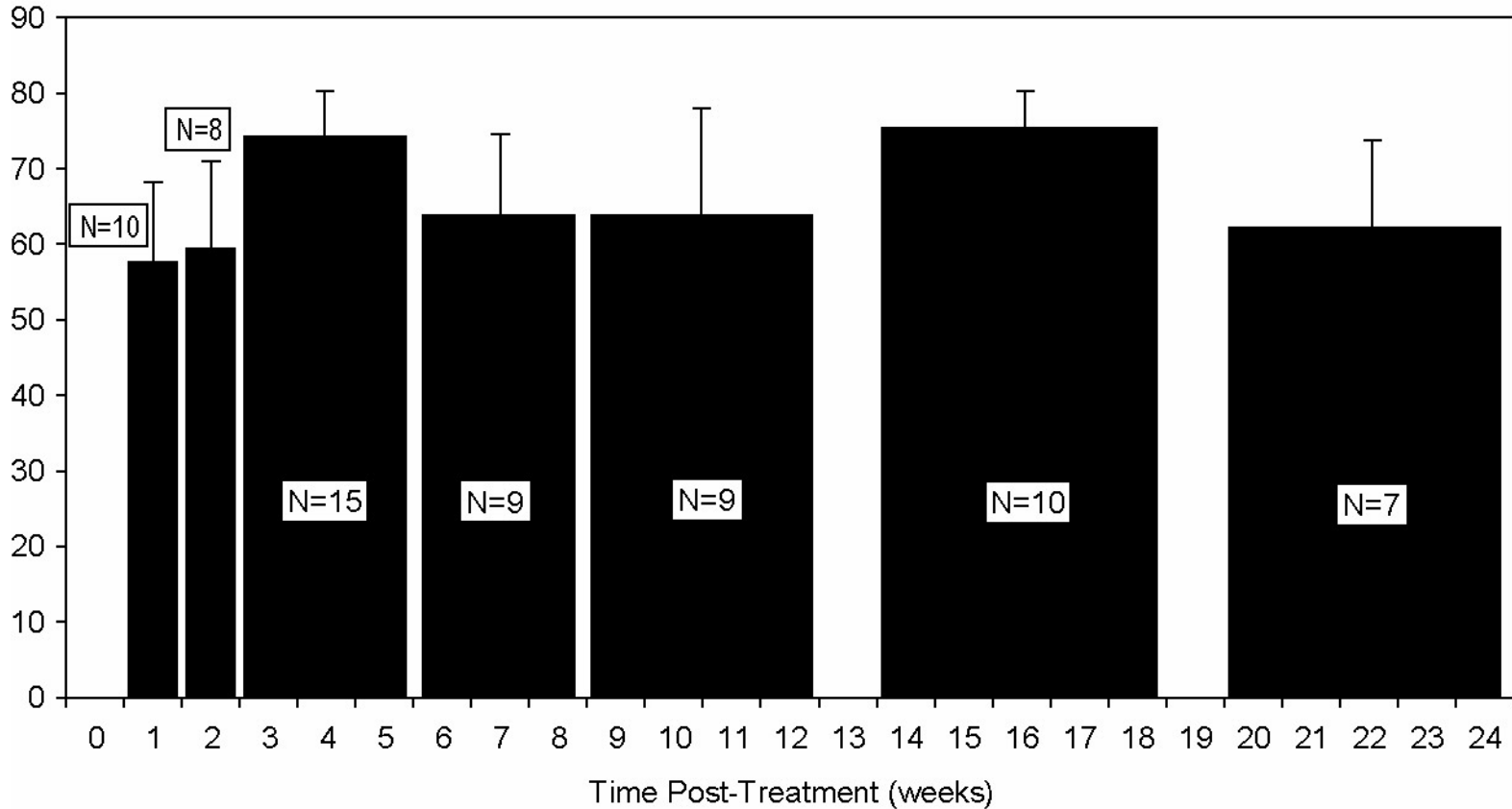


$$\% \text{Decrease} = \frac{\text{score at } t=0 - \text{score at } t}{\text{score at } t=0} \times 100$$



# Verapamil Study No. 1 (0.2 mg)

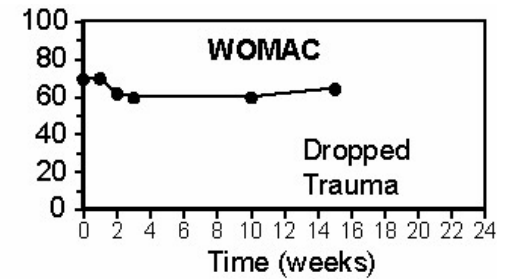
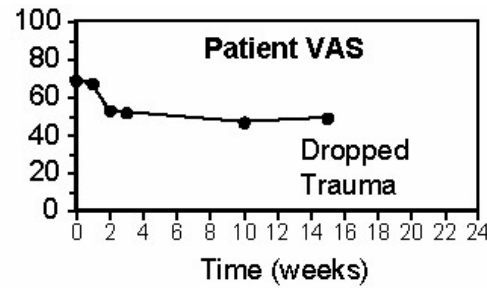
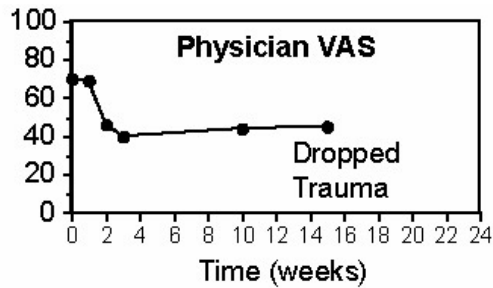
## % Decrease in Patient VAS



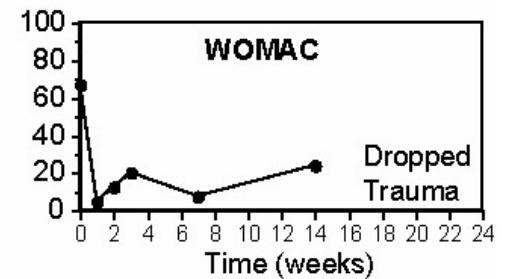
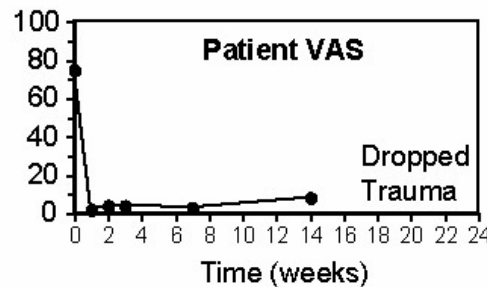
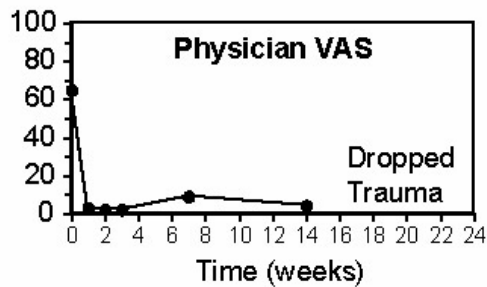
$$\% \text{Decrease} = \frac{\text{score at } t=0 - \text{score at } t}{\text{score at } t=0} \times 100$$

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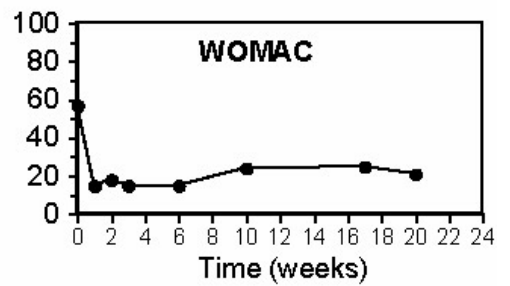
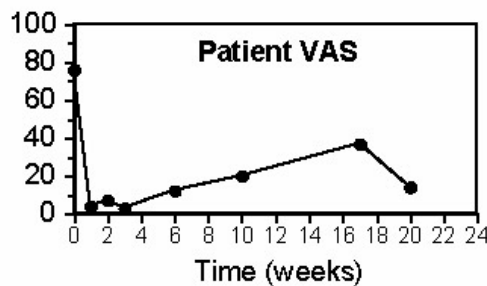
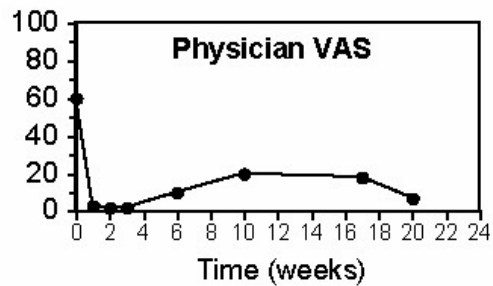
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49F  
(2-1)



Pt. No. 2  
64F  
(2-2)

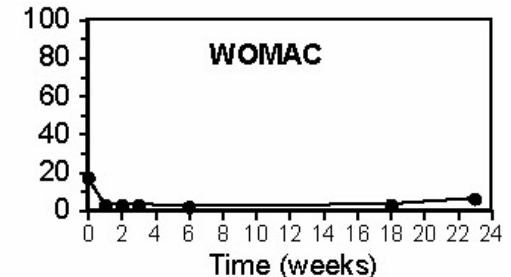
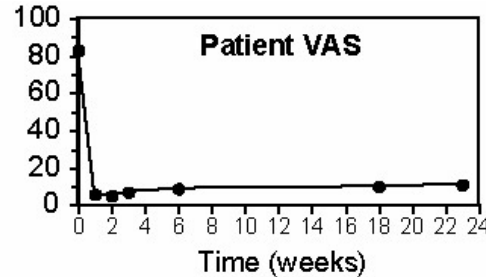
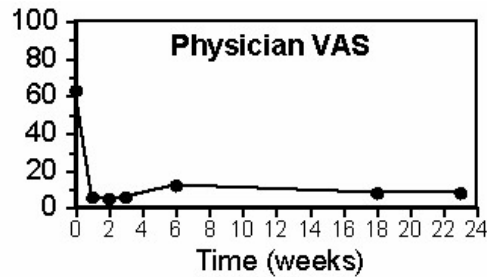


Pt. No. 3  
75F  
(2-3)

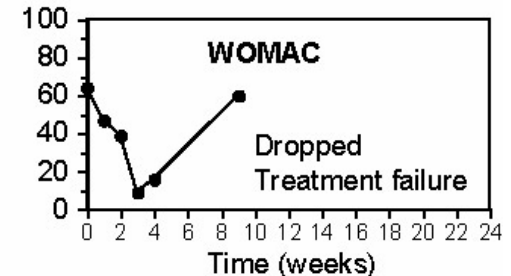
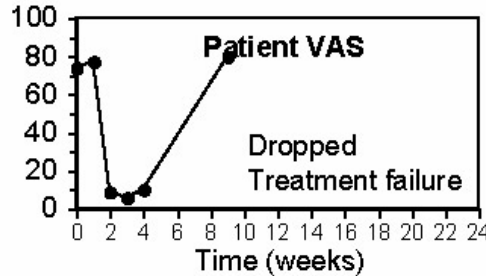
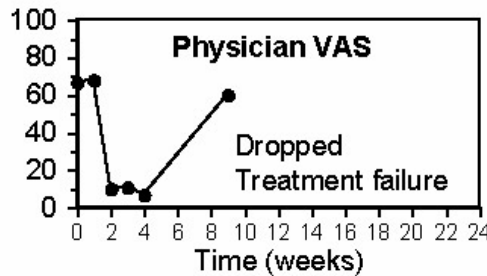


# Verapamil Study No. 2 (0.5 mg)

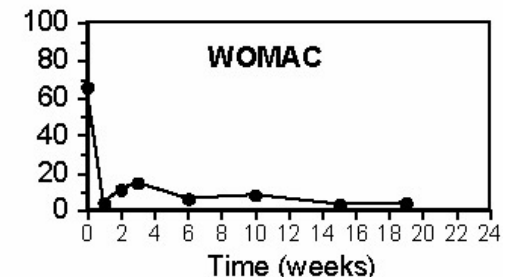
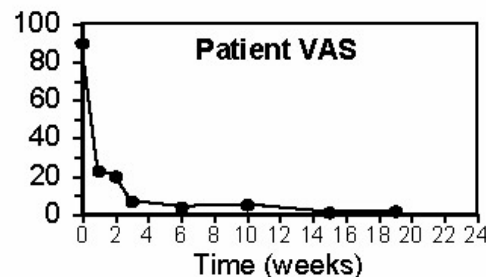
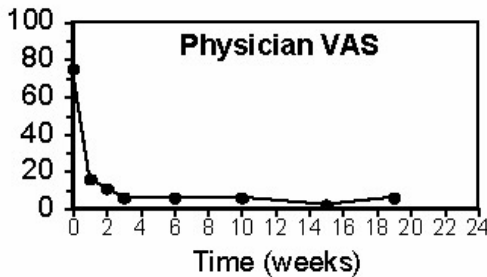
Pt. No. 4  
42M  
(2-4)



Pt. No. 5  
68M  
(2-5)

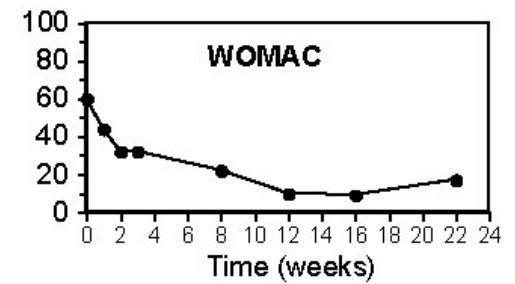
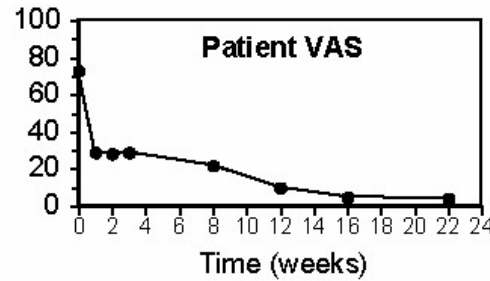
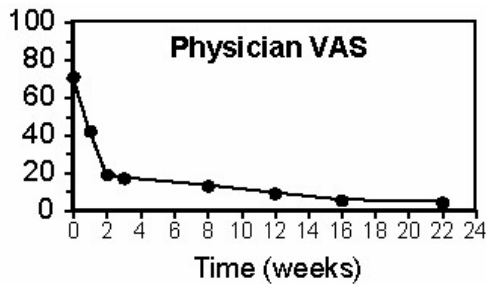


Pt. No. 6  
67F  
(2-6)

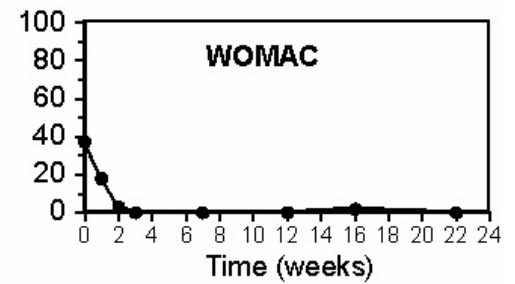
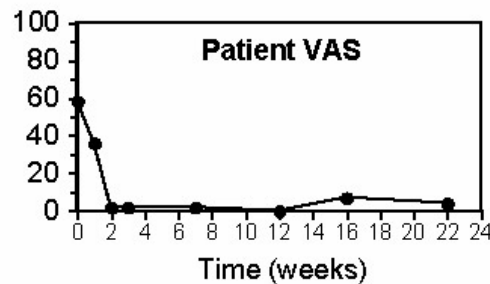
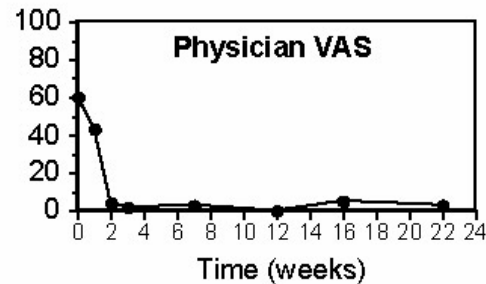


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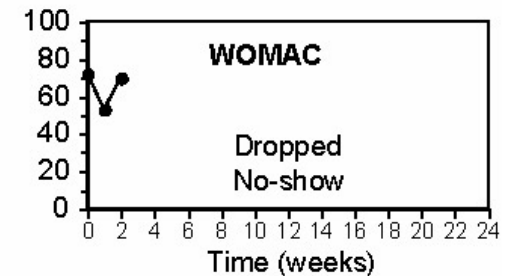
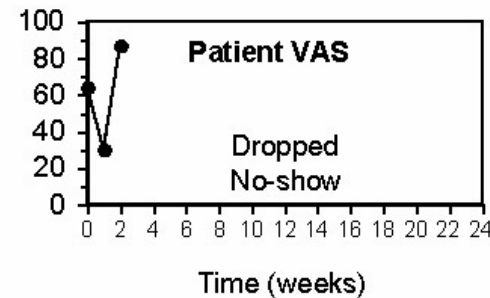
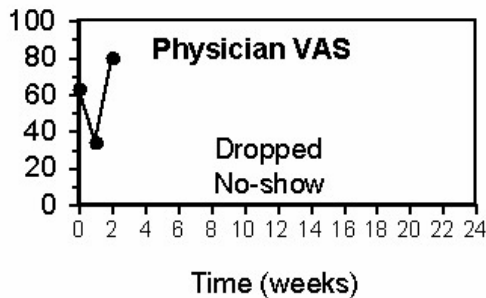
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(2-7)



Pt. No. 8  
55M  
(2-8)

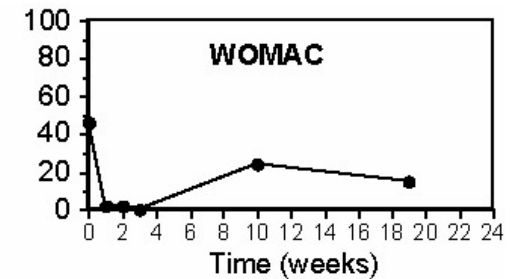
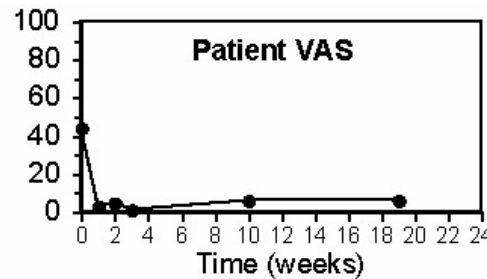
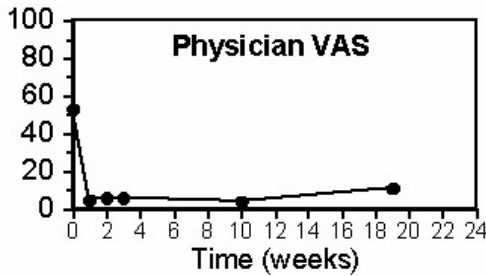


Pt. No. 9  
41M  
(2-9)

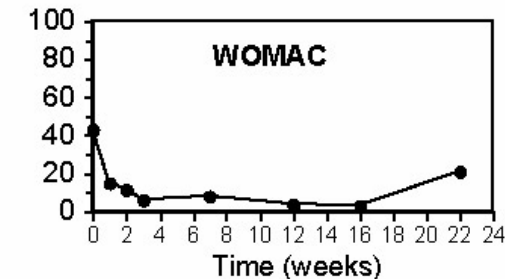
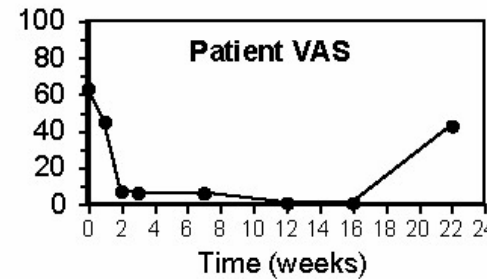
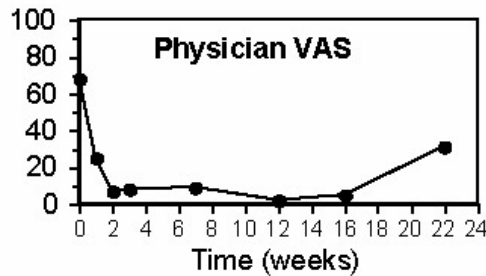


# Verapamil Study No. 2 (0.5 mg)

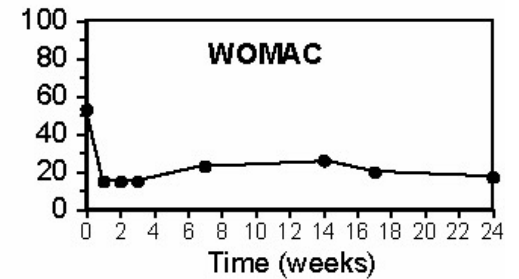
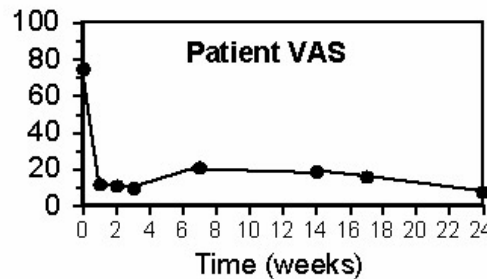
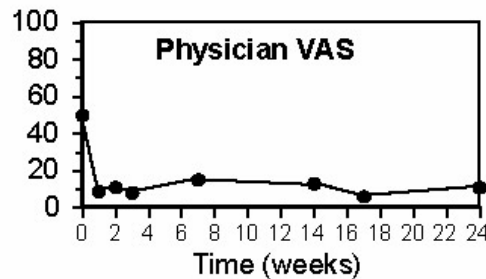
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64F  
(2-10)



Pt. No. 11  
67F  
(2-11)

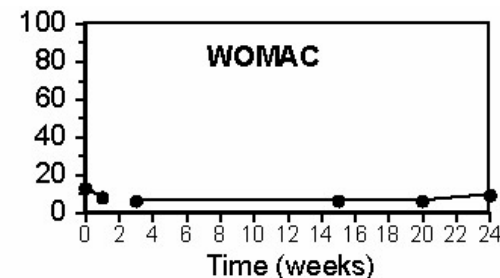
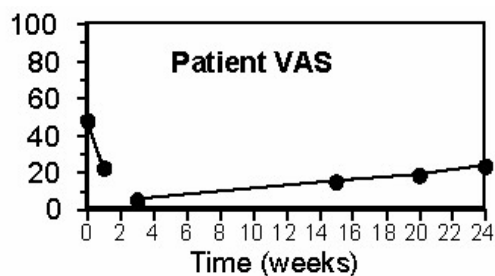
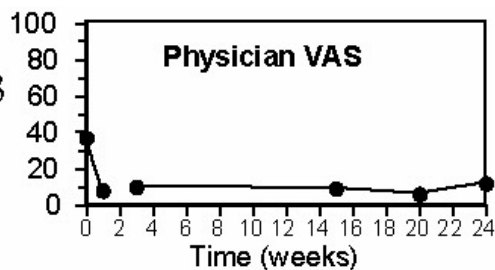


Pt. No. 12  
75F  
(2-12)

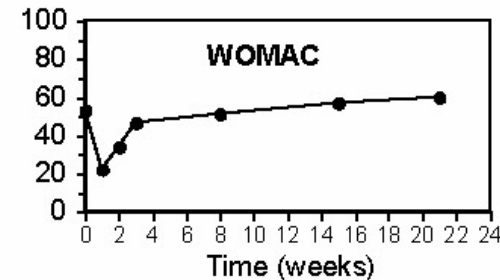
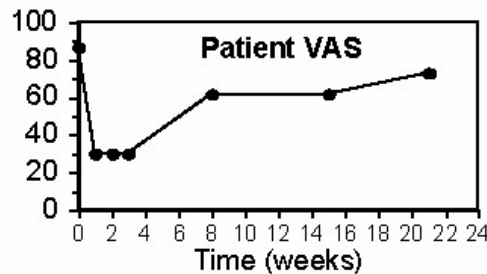
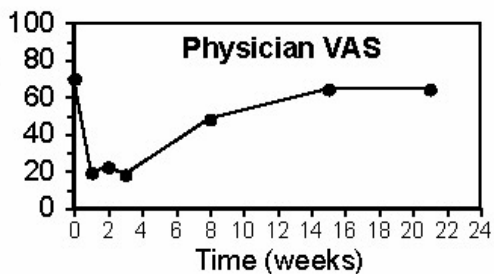


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Pt. No. 13  
42M  
(2-13)

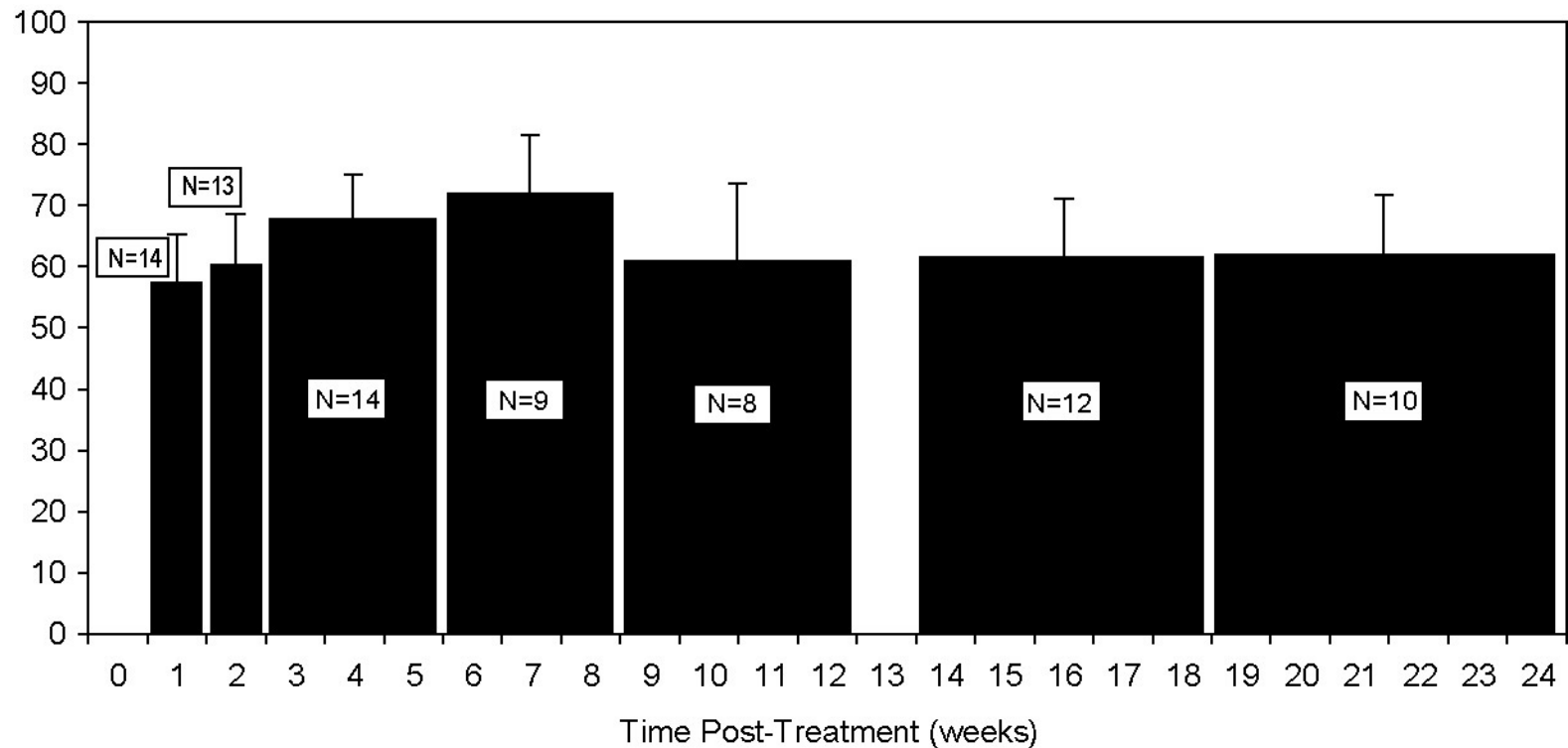


Pt. No. 14  
55F  
(2-14)



# Verapamil Study No. 2 (0.5 mg)

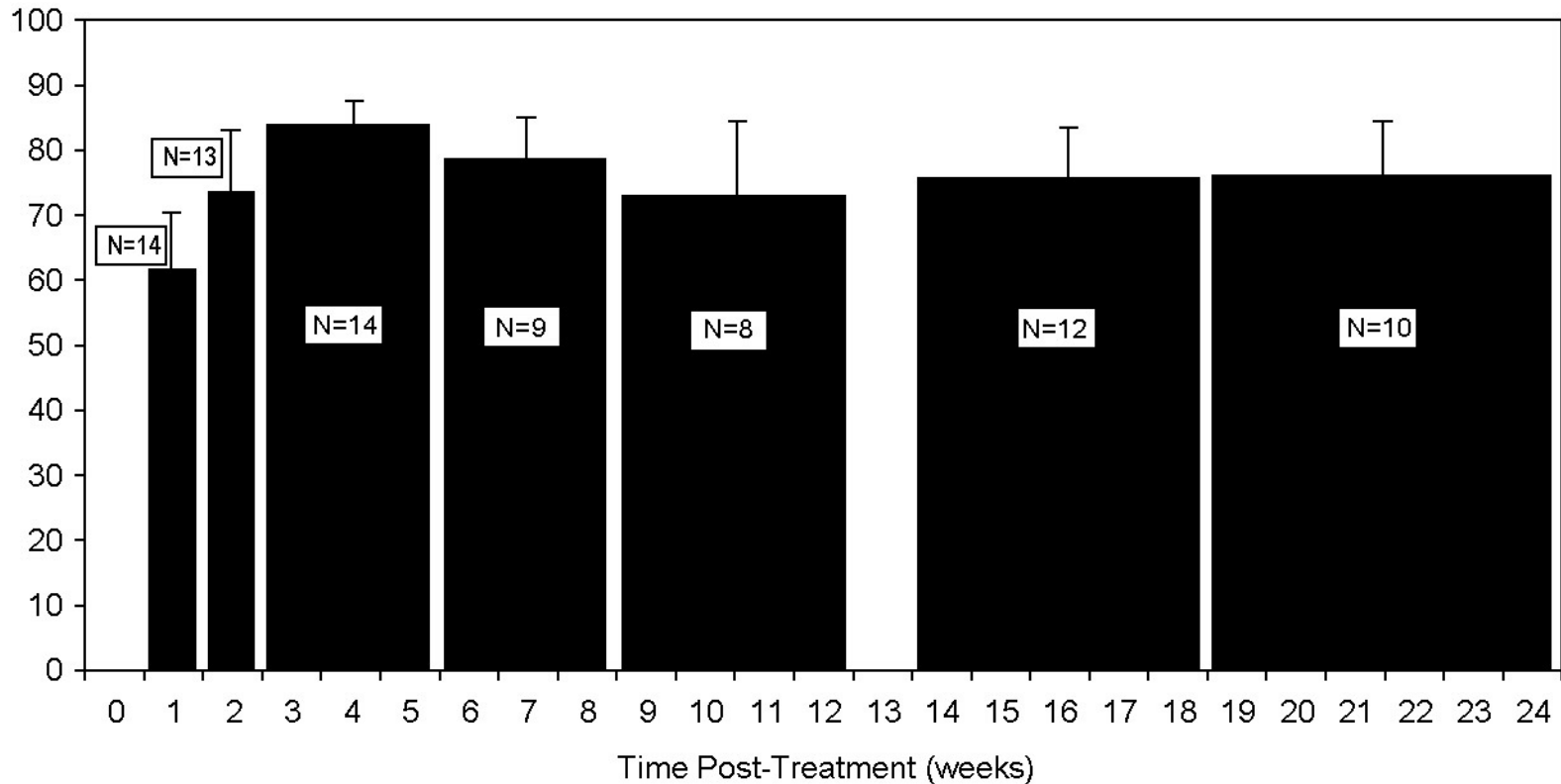
## % Decrease in WOMAC



$$\% \text{Decrease} = \frac{\text{score at } t=0 - \text{score at } t}{\text{score at } t=0} \times 100$$

# Verapamil Study No. 2 (0.5 mg)

## % Decrease in Physician VAS

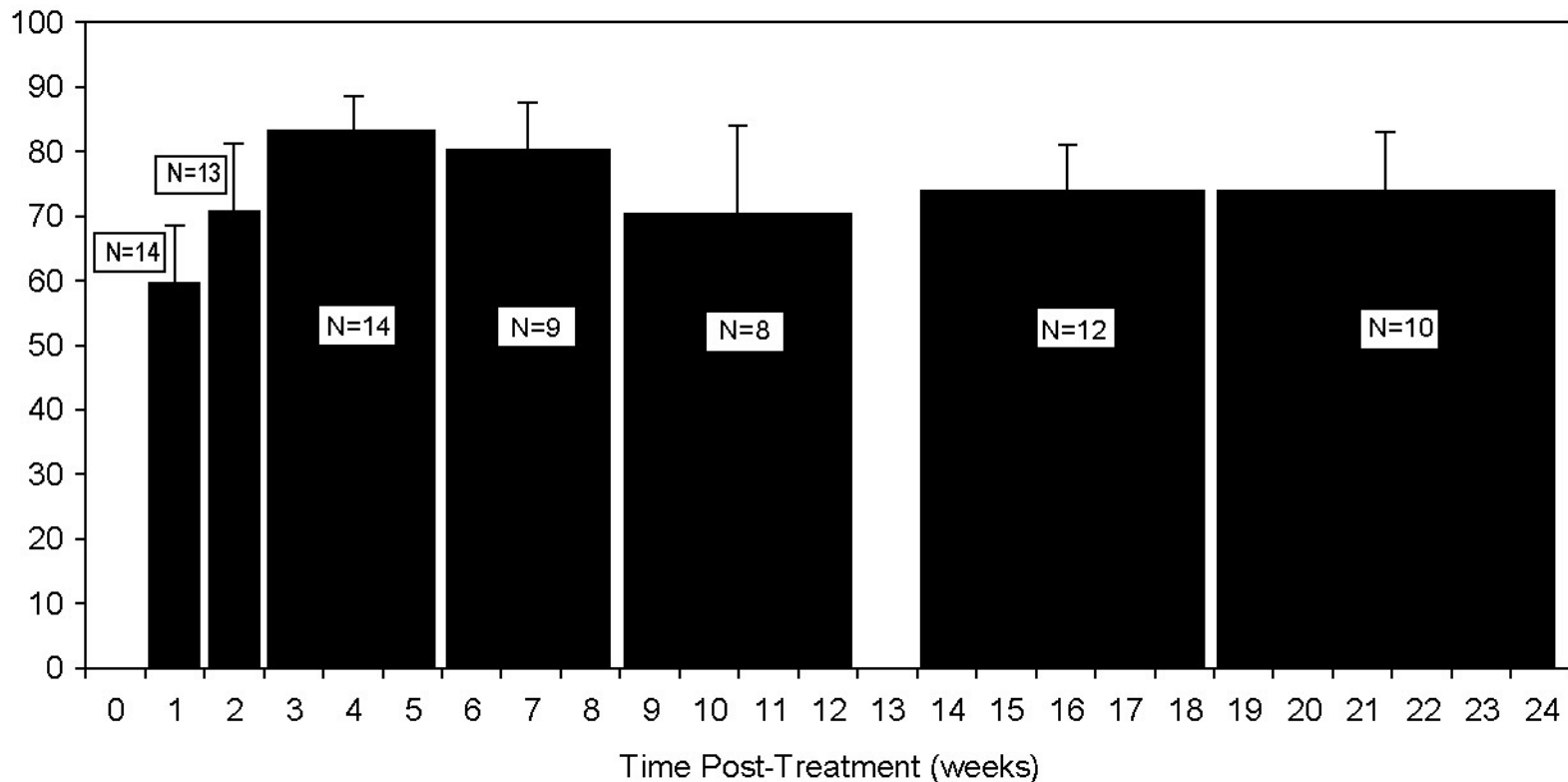


$$\% \text{Decrease} = \frac{\text{score at } t=0 - \text{score at } t}{\text{score at } t=0} \times 100$$



# Verapamil Study No. 2 (0.5 mg)

## % Decrease in Patient VAS



$$\% \text{Decrease} = \frac{\text{score at } t=0 - \text{score at } t}{\text{score at } t=0} \times 100$$

# Verapamil Study

## Summary of Results

- Pilot study
- 25 patients
- Experienced physician
- ALL data points shown
- All 3 efficacy tools suggest positive results

# Pertinent Clinical Facts:

- Most hyaluronans are tested in patients with Kellgren-Lawrence Grade 2 and 3 disease.
- Pilot study showed efficacy of verapamil in knees that were mostly Kellgren-Lawrence Grade 4.

# Important Features of the Verapamil Treatment

- Single-injection local therapy for a local disease.
- No adverse events noted in the 25-patient pilot study (no blood-pressure changes, flares, or other complications).
- Animal study indicates Verapamil is safe for intra-articular injection.
- Proposed treatment is rationally grounded.
- Verapamil is generally recognized as safe.

# What is the Market Looking For?

- A single-injection therapy for osteoarthritis has many benefits.
- Physicians and patients prefer simplified therapies.
- One injection q 3-4 months

# Single Injection of Verapamil for the Treatment of Osteoarthritis

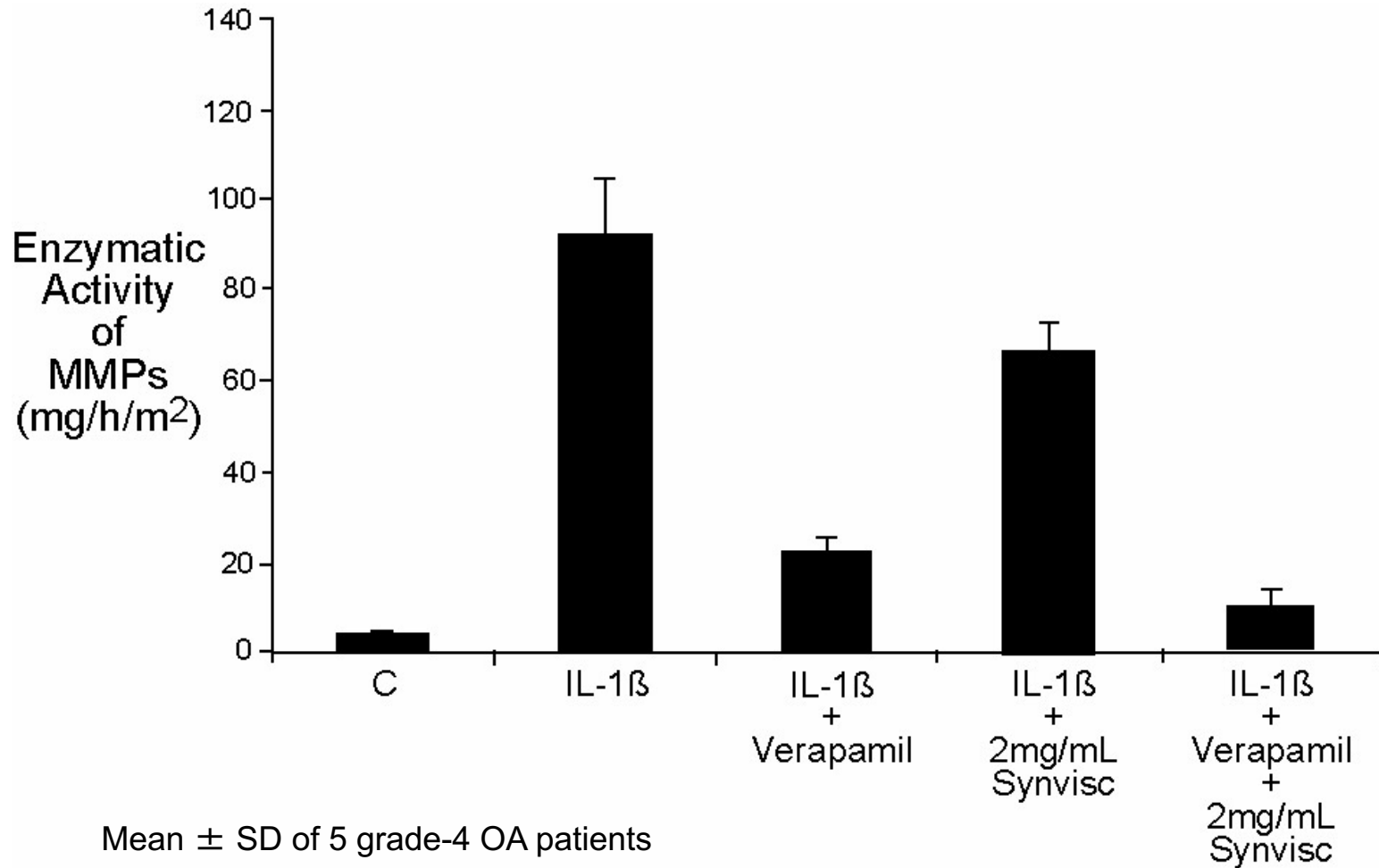
- Local therapy for local symptoms
- Local therapy avoids systemic adverse events.
- Verapamil is technically easier to inject than ANY hyaluronan.

# Verapamil Composition

Are anti-inflammatory effects of verapamil and Synvisc additive?

# Effects of Synvisc and Verapamil are Additive

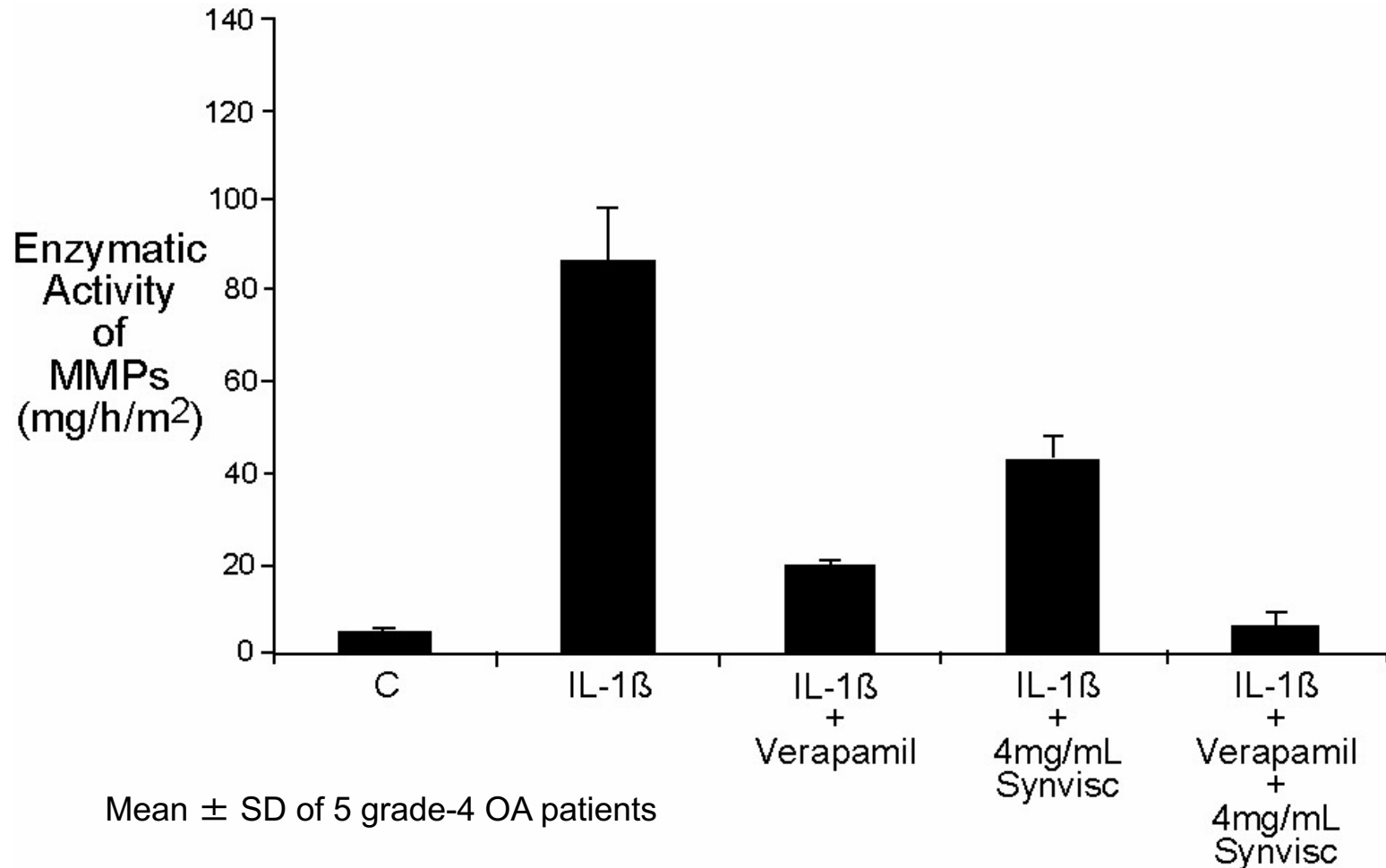
## Synvisc Concentration 2 mg/mL





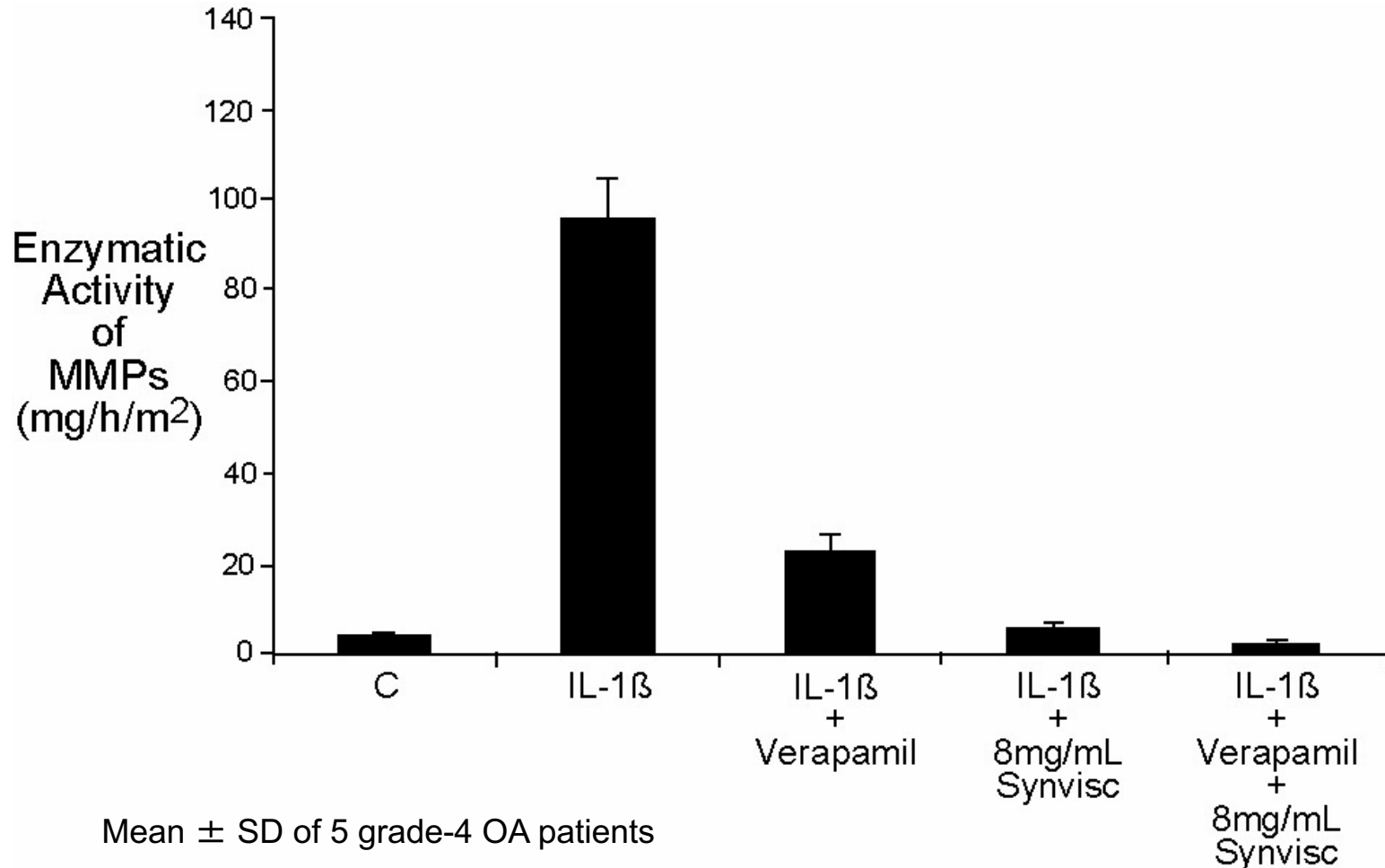
# Effects of Synvisc and Verapamil are Additive

## Synvisc Concentration 4 mg/mL



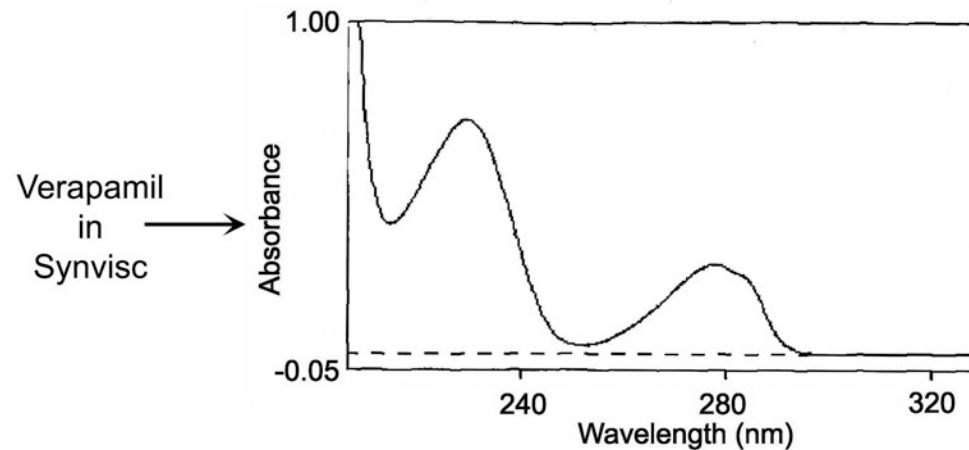
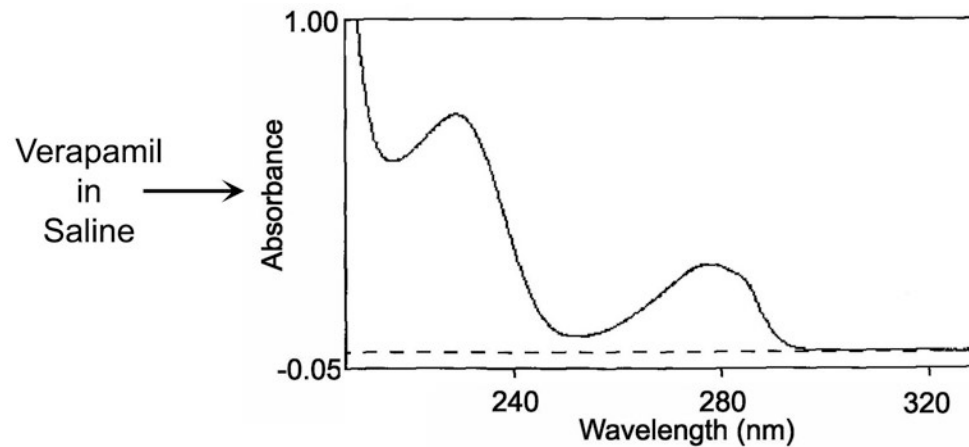
# Effects of Synvisc and Verapamil are Additive

## Synvisc Concentration 8 mg/mL



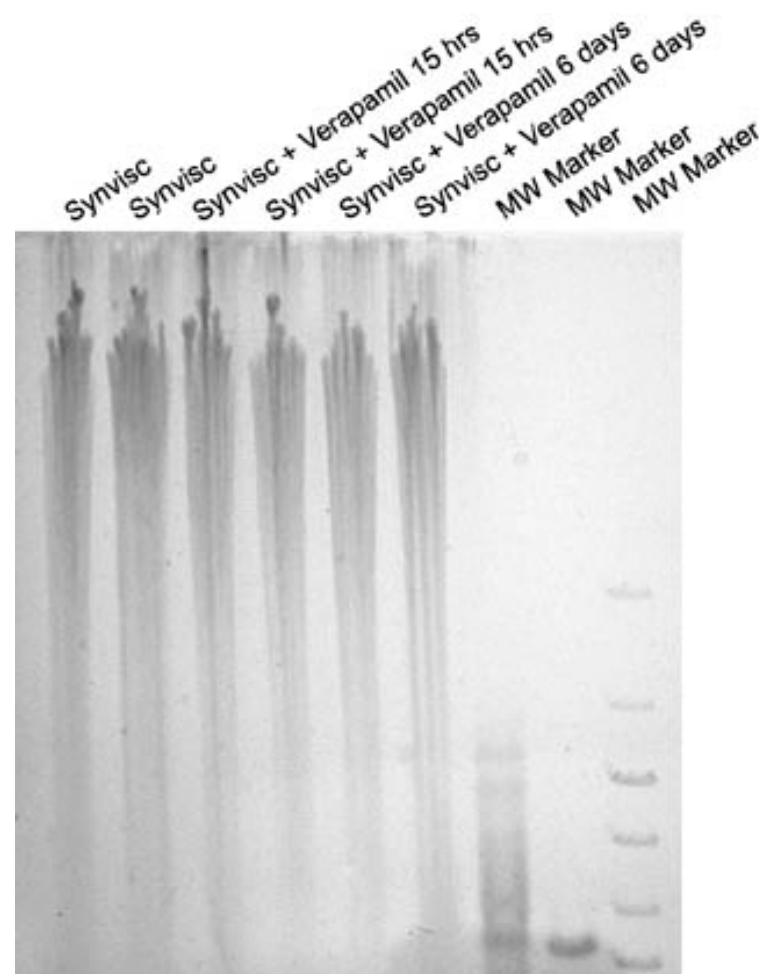
# Compatibility of Verapamil and Synvisc

## Effect of Synvisc on Verapamil



# Compatibility of Verapamil and Synvisc

## Effect of Verapamil on Synvisc



# Open Study Evaluating Verapamil Plus Synvisc in Osteoarthritis of the Knee

IRB ..... LSUHSC-S

Study Design ..... Open study (no contemporaneous control)

Principal Investigator .... David Waddell, M.D.

Other Investigators ..... None

Study Location ..... OSL

Dose ..... 0.5 mg Verapamil + Synvisc, x3

Inclusion Criteria ..... OA-IV

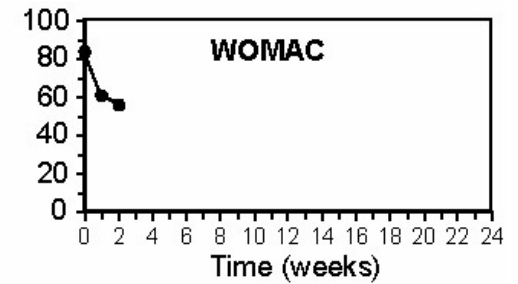
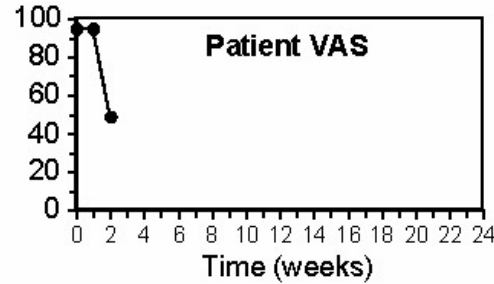
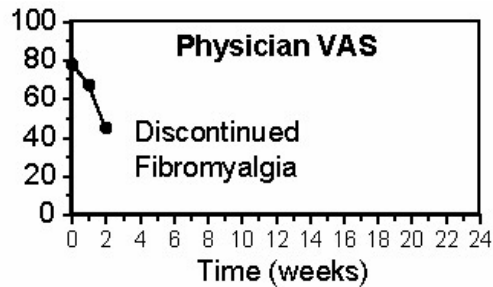
Study Hypothesis ..... Symptomatic treatment of OA pain

Study Endpoints ..... WOMAC, Physician VAS, Patient VAS

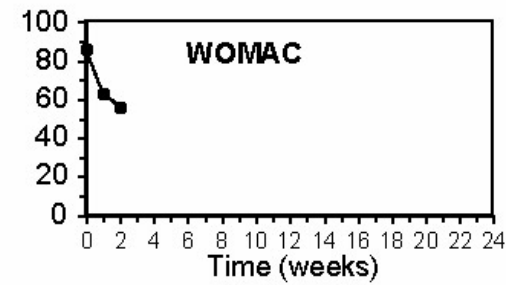
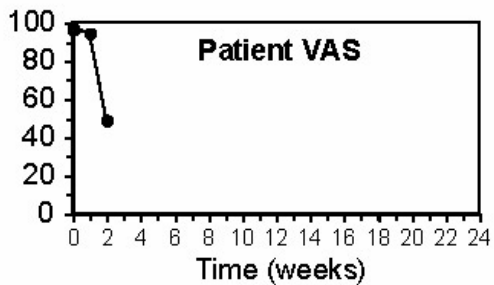
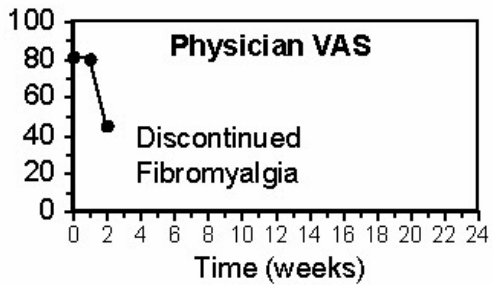
Follow-up Schedule ..... 1, 2, 3, 4, 5, 16, 20 weeks

# Verapamil + Synvisc Study

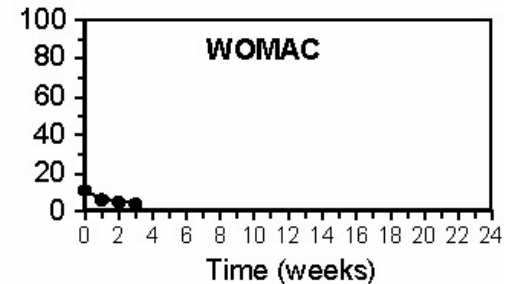
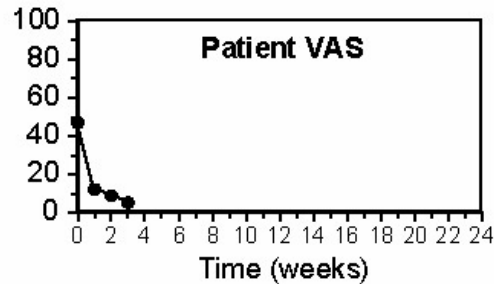
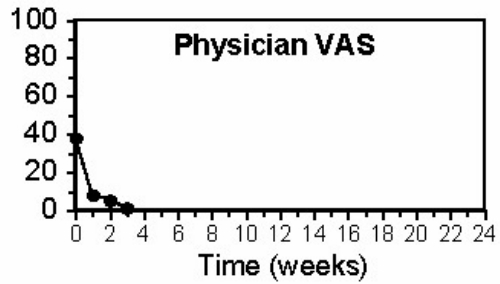
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67F  
(4-1)



Pt. No. 2  
67F  
(4-2)

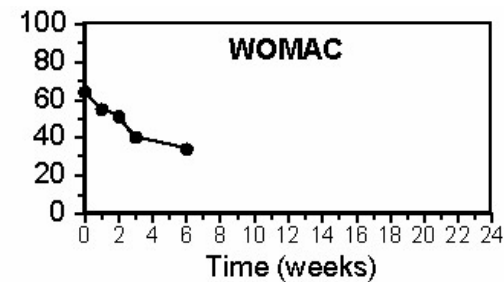
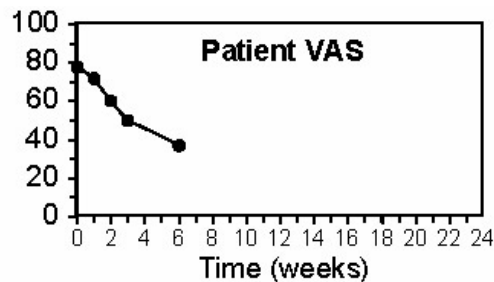
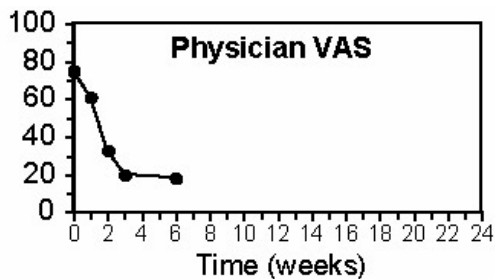


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70M  
(4-3)

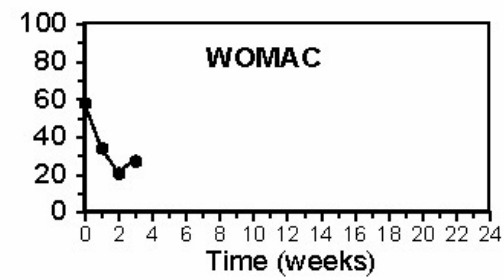
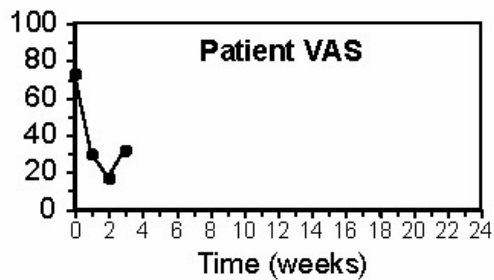
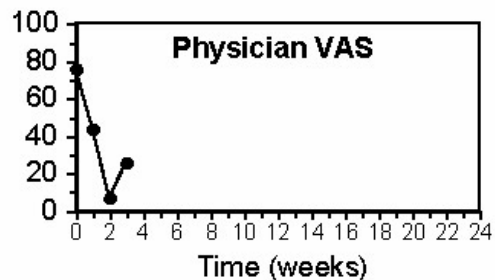


# Verapamil + Synvisc Study

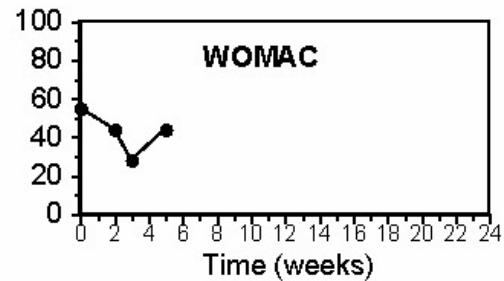
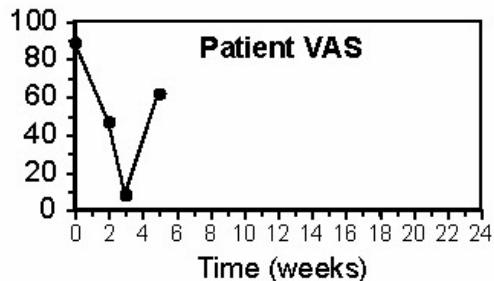
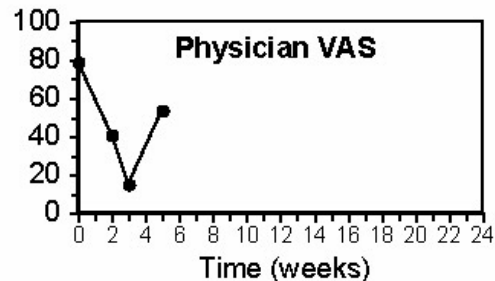
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76F  
(4-5)



Pt. No. 6  
69F  
(4-6)

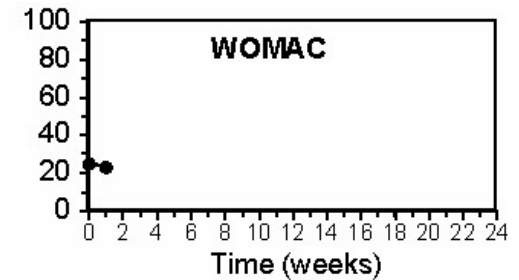
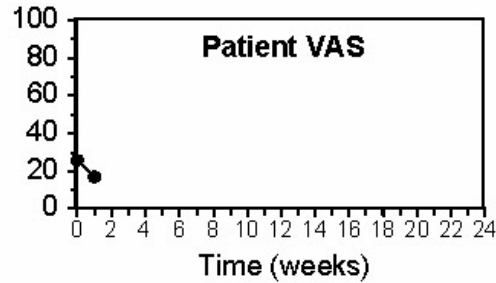
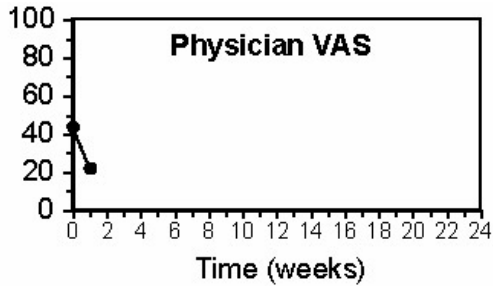


Pt. No. 7  
73F  
(4-7)

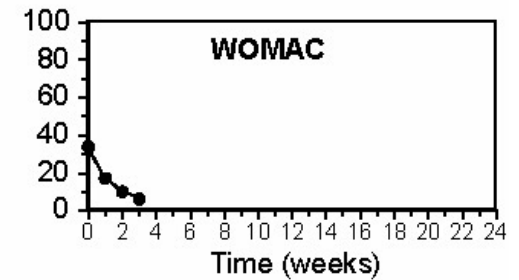
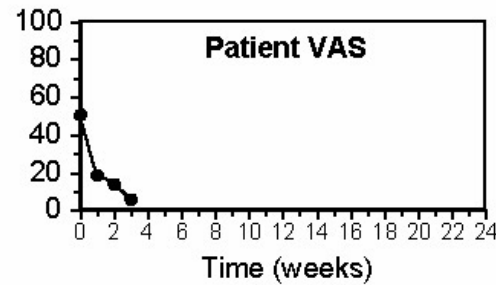
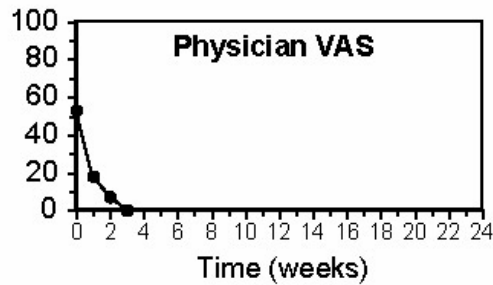


# Verapamil + Synvisc Study

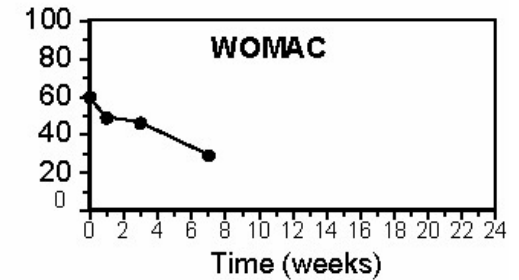
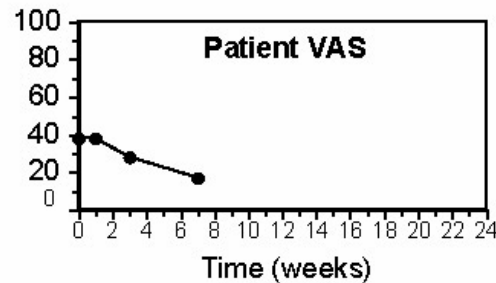
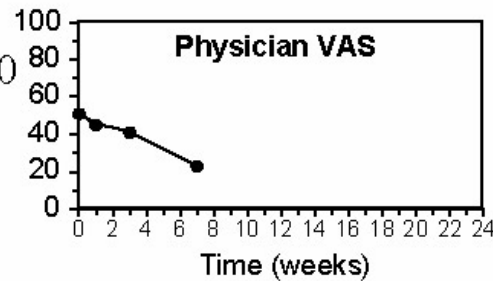
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59M  
(4-8)



Pt. No. 9  
66F  
(4-9)



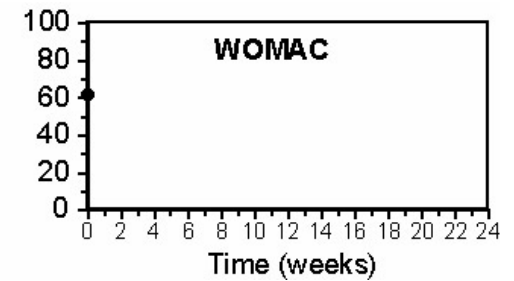
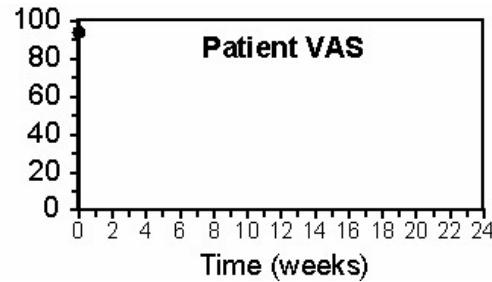
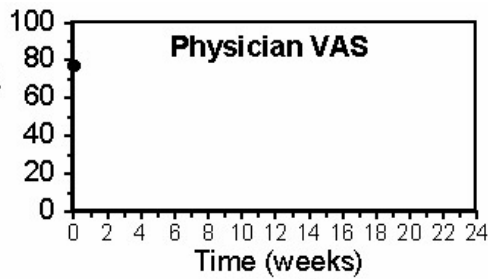
Pt. No. 10  
73F  
(4-10)





# Verapamil + Synvisc Study

Pt. No. 12  
64M  
(4-12)



# Effect of Verapamil on Flare Probability

<u>Patient</u>	<u>No. of Previous Courses</u>	<u>No. of Injections Verapamil/ Synvisc</u>	<u>Injection-Wise Probability of a Flare</u>
1 (3-1)	2	1	0.08
2 (3-2)	1	1	0.06
3 (3-3)	1	1	0.06
4 (3-4)	1	1	0.06
5 (3-5)	1	1	0.06
6 (4-1)	2	3	0.08, 0.01, 0.005
7 (4-2)	2	3	0.08, 0.01, 0.005
8 (4-3)	1	3	0.06, 0.02, 0.01
9 (4-4)	1	3	0.06, 0.02, 0.01
10 (4-5)	3	3	0.10, 0.03, 0.03
11 (4-6)	1	3	0.06, 0.02, 0.01
12 (4-7)	2	3	0.08, 0.01, 0.005
13 (4-8)	3	2	0.10, 0.03
14 (4-9)	1	3	0.06, 0.02, 0.01
15 (4-10)	1	3	0.06, 0.02, 0.01
16 (4-11)	3	1	0.10
<b>Mean Probability</b>			<b>0.041</b>

Number of knee injected: 35

Number of flares: 0

Probability of at least one flare in 35 injections in absence of Verapamil: 78%

# U.S. Patents Pending

- U.S. Patent Application No. 11/138,738  
COMPOSITIONS FOR TREATING  
OSTEOARTHRITIS
- U.S. Patent Application No. 11/138,744  
METHODS FOR TREATING  
OSTEOARTHRITIS

# Future Plans

Pilot studies show:

- (1) strong positive evidence that a single injection of verapamil is therapeutic in the treatment of osteoarthritis, and
- (2) addition of verapamil to Synvisc may block the flare.

Appropriate clinical studies that capitalize on these findings are warranted.