Low Dose Naltrexone: A Novel Therapy for Inflammatory Bowel Disease

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OBJECTIVES

- Background: opioids & receptors
- Role of the opioid system in inflammation/ cancer
- Hypotheses Regarding Mechanism of Action
- Clinical Trials

Inflammatory Bowel Disease

Cancer

Endogenous Opioid Peptides

- Play a role in neurotransmission
- Serve as potent regulators of growth
- Influence cells undergoing cellular repair
- Augment the immune system
- Induce feeling of overall well-being

(i.e. euphoria, runner's high)

Opioid Peptides and Receptors

Endogenous Opioids

- Enkephalin
- [Met^5]-enkephalin
- Endorphin
- leu-enkephalin
- dynorphin

- Euphoria
- Runner's high

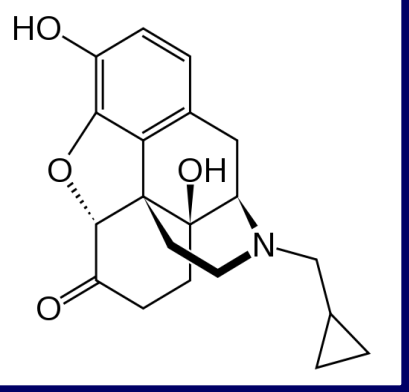
Synthetic Opiates

- Morphine
- Demerol
- Codeine
- Darvon
- Fentanyl
- Methadone +/-

- Pain
- Sedation
- Diarrhea

Opioid Receptors

Name	Ligand	Location	Function
mu (μ)	Morphine & opiates, low affinity enkephalin	Plasma Membrane	Analgesia, respiration, GI motility, inflammation
Delta (δ)	Enkephalin High affinity	Plasma Membrane	Analgesia, inflammation
Kappa (κ)	Ethylketo-cyclazocine	Plasma Membrane	Analgesia, diuresis, inflammation
OGFr	[Met^5]-enkephalin	Nuclear	Growth, Healing



Naltrexone

Small 377 Mwt

- A nonspecific long-acting opioid receptor antagonist
- Decreases TNF-α and other inflammatory cytokines from inflammatory cells
- Approved by FDA at the 50 mg dose for alcohol withdrawal syndromes
- Generic
- Inexpensive

Synthetic Antagonists and Agonists

Antagonists

- **Nonselective:**
  - Naltrexone (NTX) & Naloxone
- **Delta:**
  - δ1 BNTX: Benzylidene-naltrexone
  - δ2 **NTI:** naltrindole
- **Mu: Cyprodime**
- **κ : Norbinaltorphimine**

Agonists

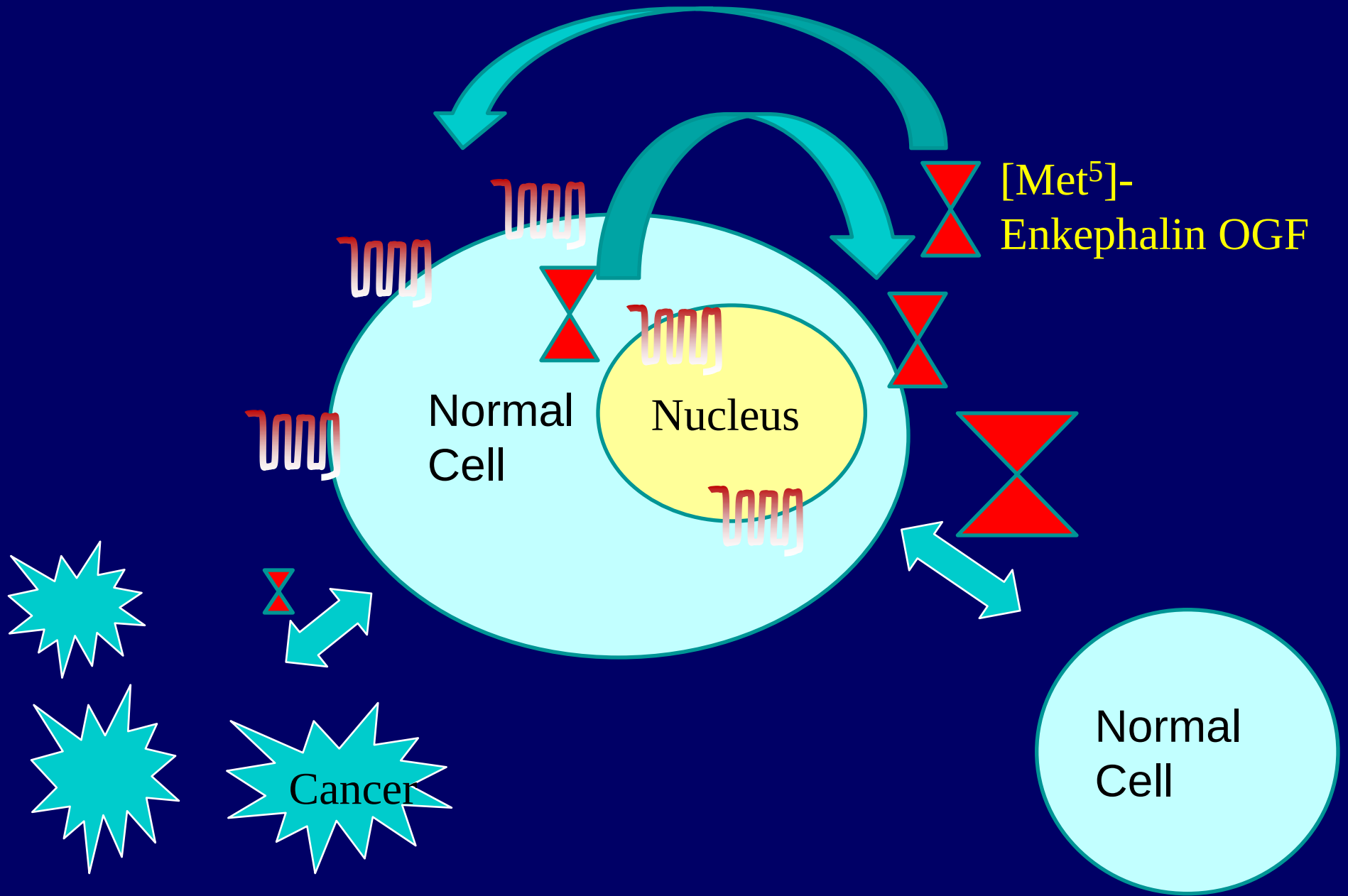
- DALDA: Mu agonist
- DAMGO: Mu agonist

Mu receptor

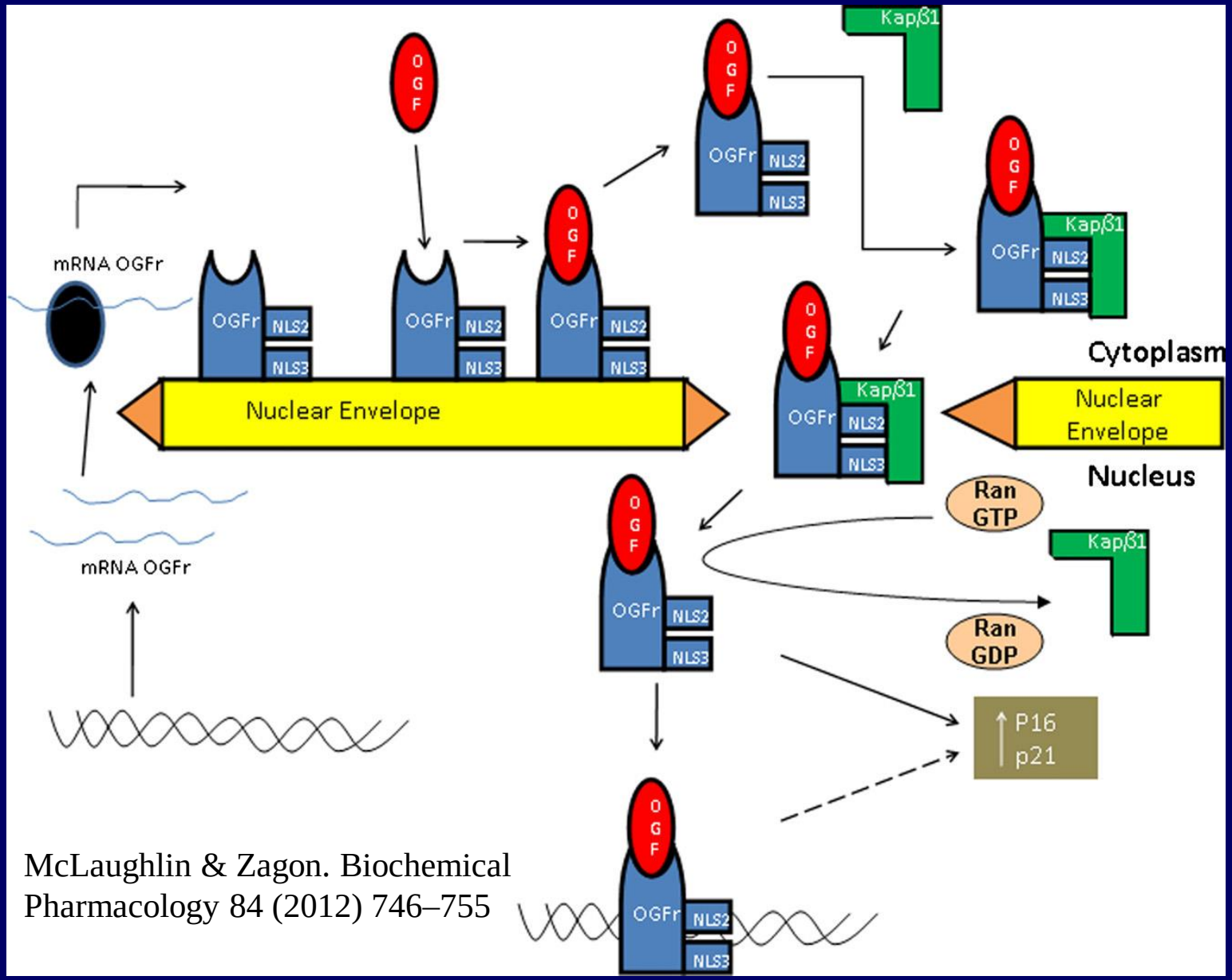
The Mu opioid receptor has

- Low affinity (attraction) for enkephalin and naltrexone
- Has opposing effects of delta and kappa receptors
- If the Mu receptor is blocked (antagonist) it can increase inflammation
- If the Mu receptor is stimulated (agonist) inflammation decreases.

Homeostasis regarding cell growth and the OGFr



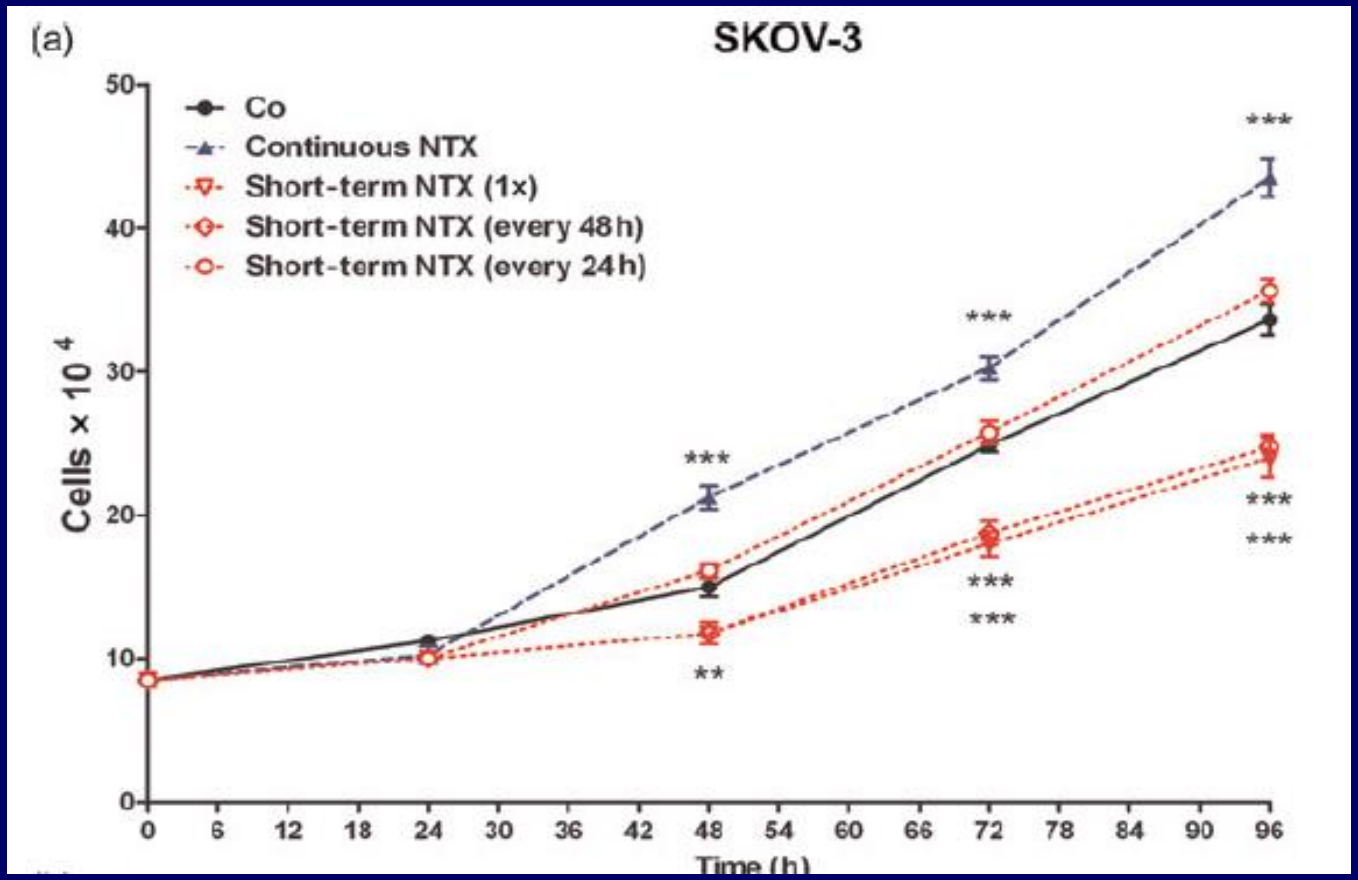
Once inside the nucleus, OGF activates the Rb pathway by upregulating p16 and/p21 which are cyclin-dependent inhibitory kinases, and thereby retards transition from G1 to S phases in the cell cycle, with delayed cell replication and ultimate cell number resulting.



McLaughlin & Zagon. Biochemical Pharmacology 84 (2012) 746–755

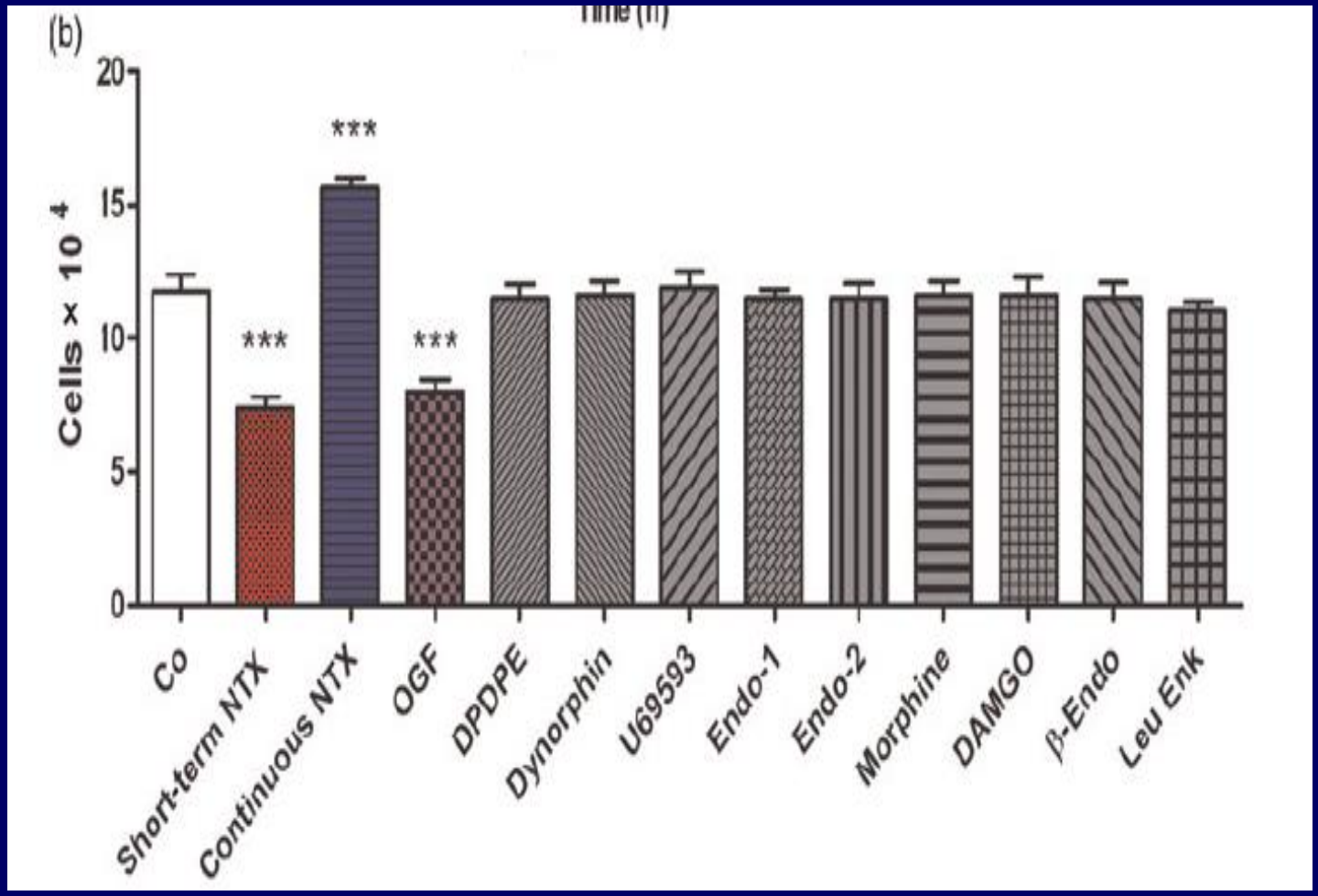
Why Low Dose NTX?

Experimental Biology and Medicine 2011, 236:1036-1050.



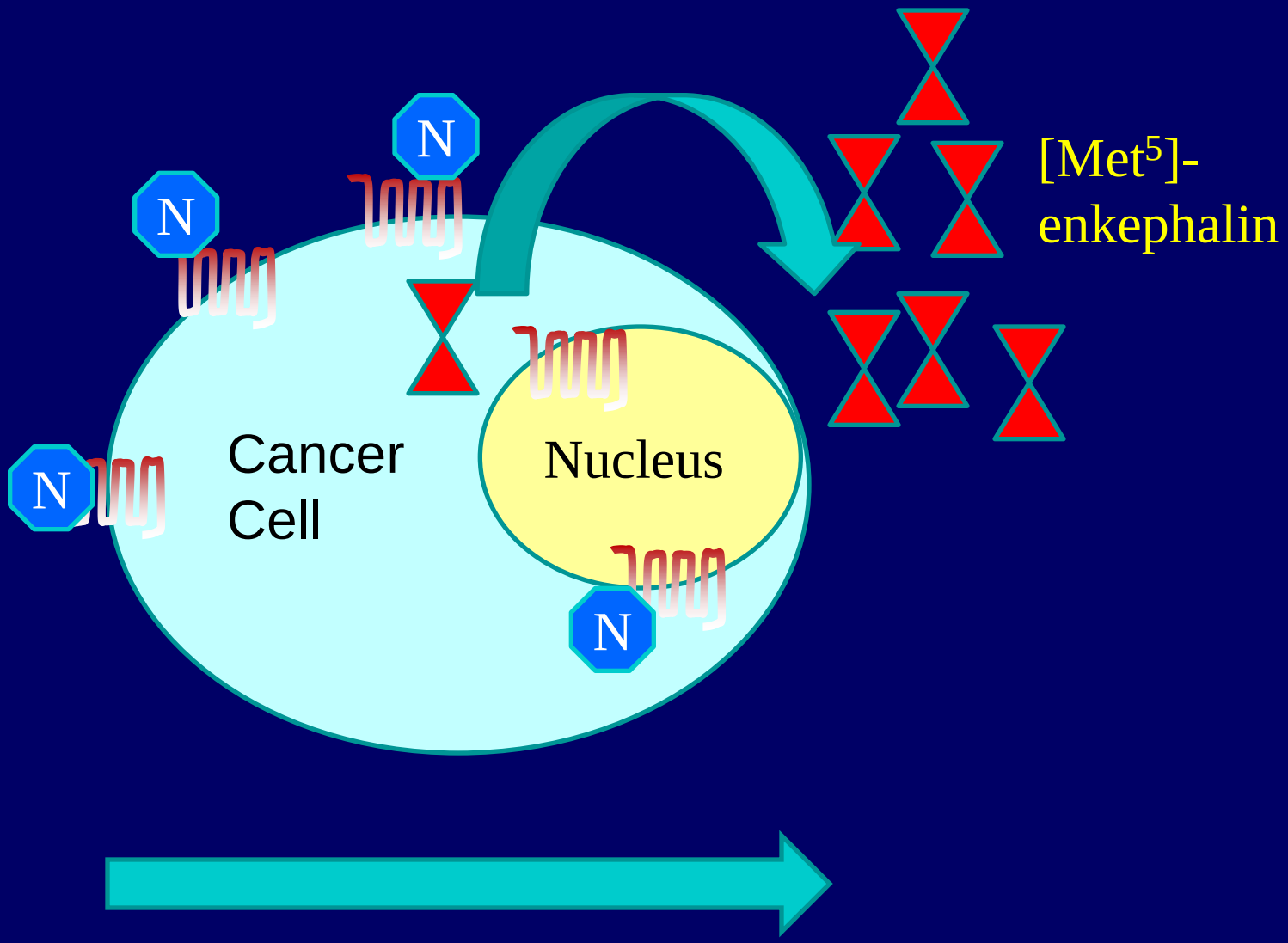
NTX 10^{-5}M x 6hr

LDN mimics OGF (enkephalin)

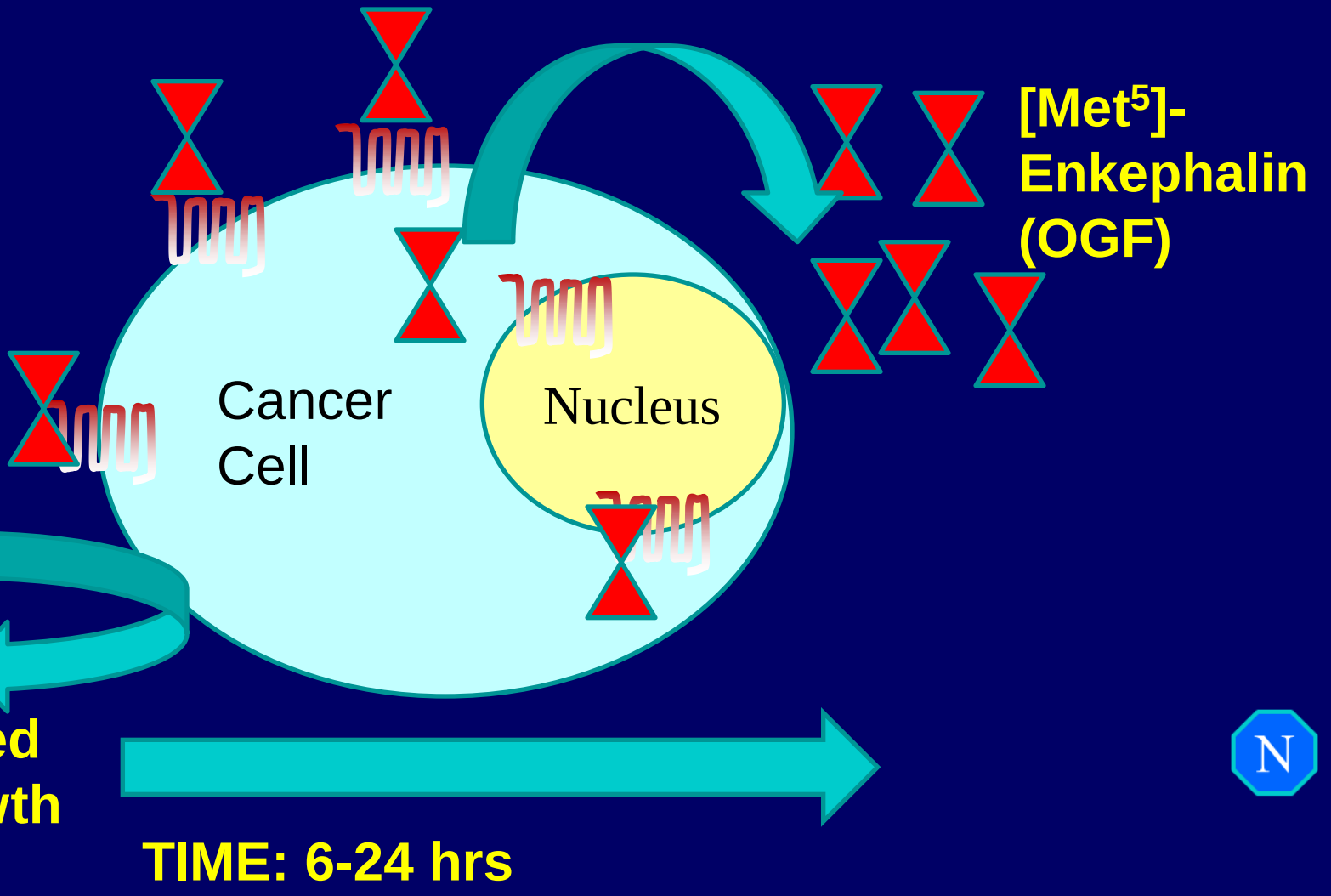


Growth is only mediated through the OGFr not Mu, Kappa, Delta

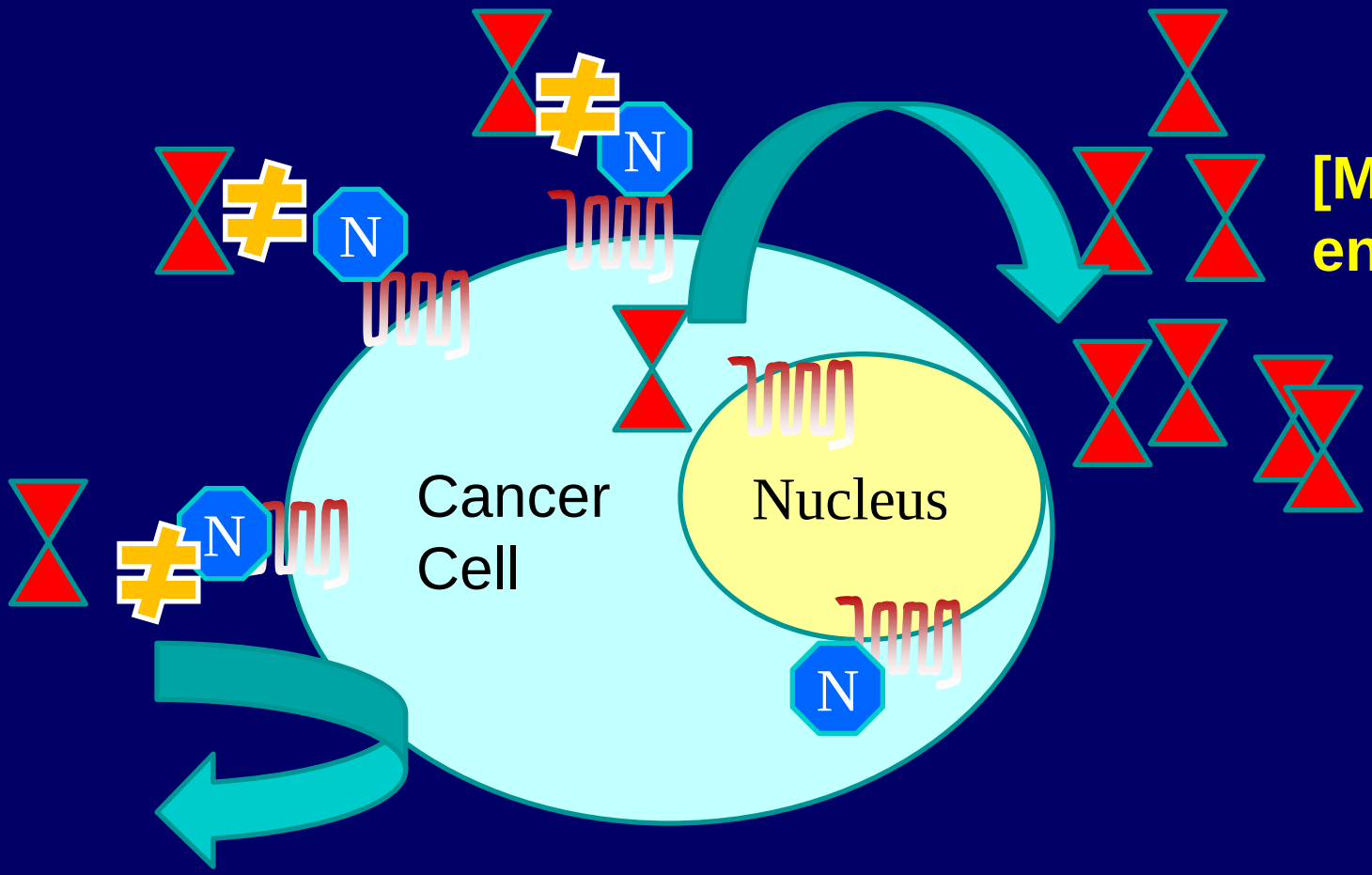
Effects of Low Dose Naltrexone



Effects of Low Dose Naltrexone



Risks if Naltrexone Dose is too High



No effect or Increased cell Growth

TIME: 6-24 hrs

Opioids and Mechanism of Action Summary

- The proposed mechanism of action of low-dose naltrexone has been evaluated in cancer cells.
- The effects of naltrexone on normal cells has been studied in animal models.
- The mechanism by which LDN works in normal cells or immune cells may be different than in cancer cells.
- Earlier studies that treated mice with neuroblastoma cancer showed that enkephalin and endorphin levels increased in the tumor tissue, not in the blood. (Zagon, Brain Res 1989).

Role for Endogenous Opioid Peptides in Inflammation

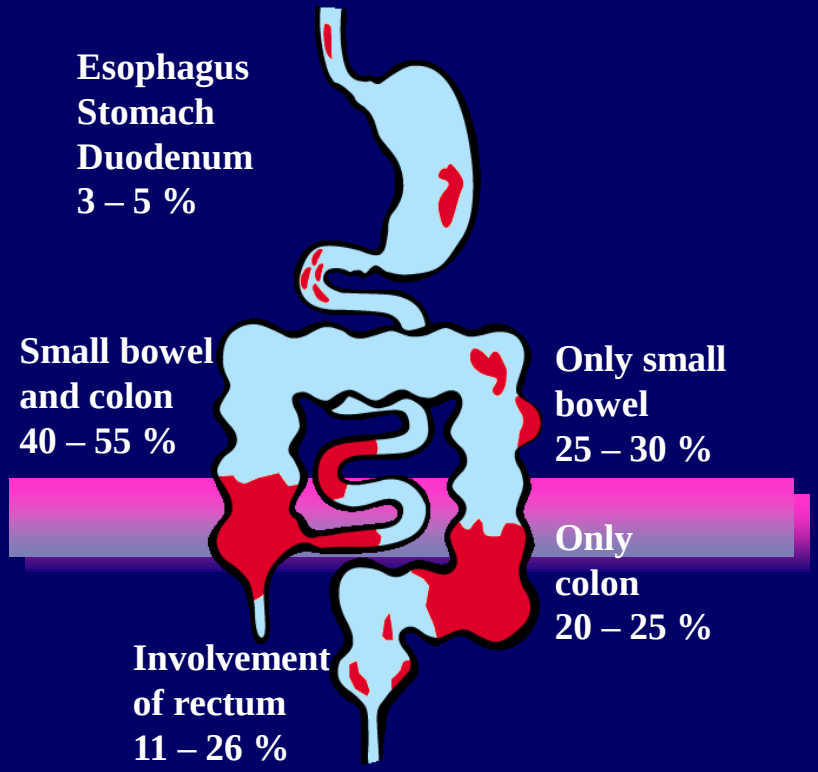
- Chronic use of narcotic analgesics significantly reduces immune cell function.
- Opiates inhibit chemokine-induced chemotaxis.
- Immune cells have been shown to express μ, κ, and δ-opioid receptors.
- Immune cells secrete opioid peptides, such as enkephalin & endorphins.

Role for Endogenous Peptides in Inflammation, Continued

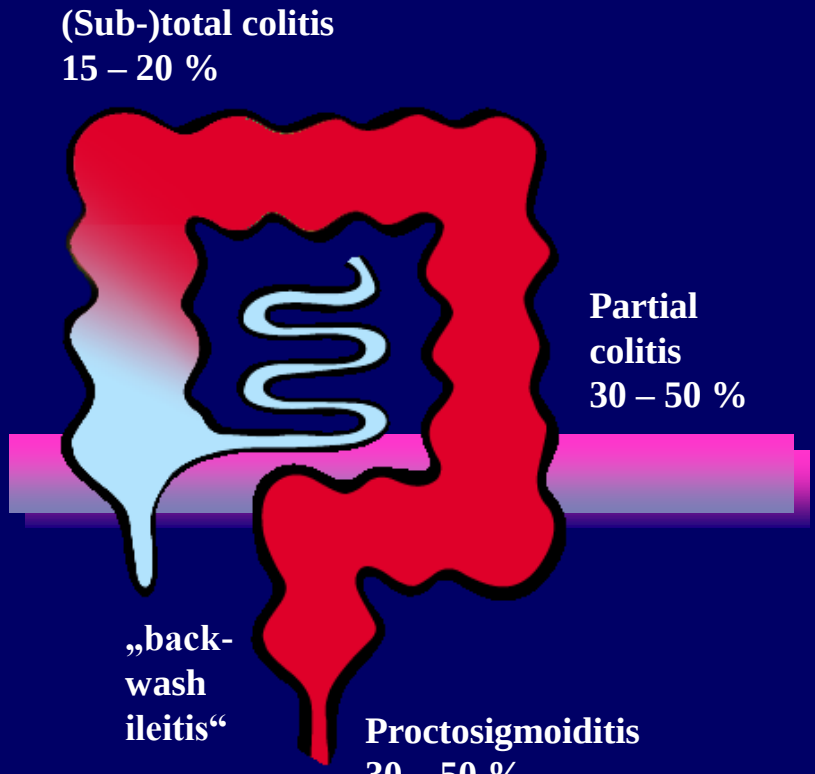
- Opioids have been shown to induce the release of pro-inflammatory cytokines, such as IL-12 and TNF-α.
- [Met^5]-enkephalin knock-out mice show a defect in T-cell activation.

Inflammatory Bowel Diseases
Crohn's Disease and Ulcerative Colitis

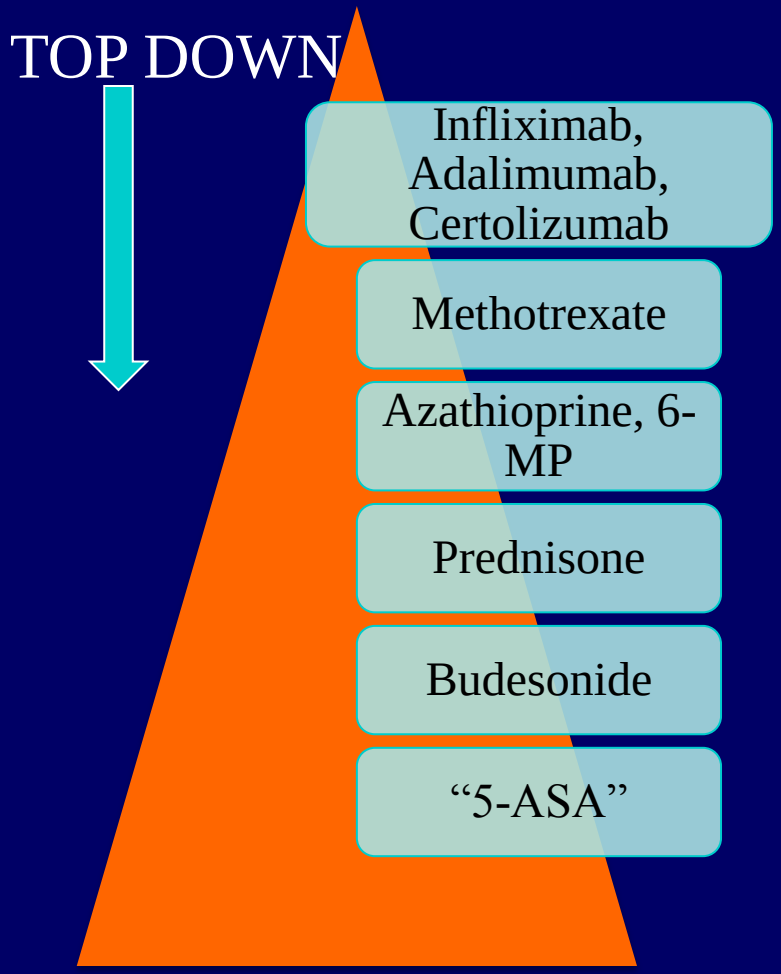
Crohn's disease



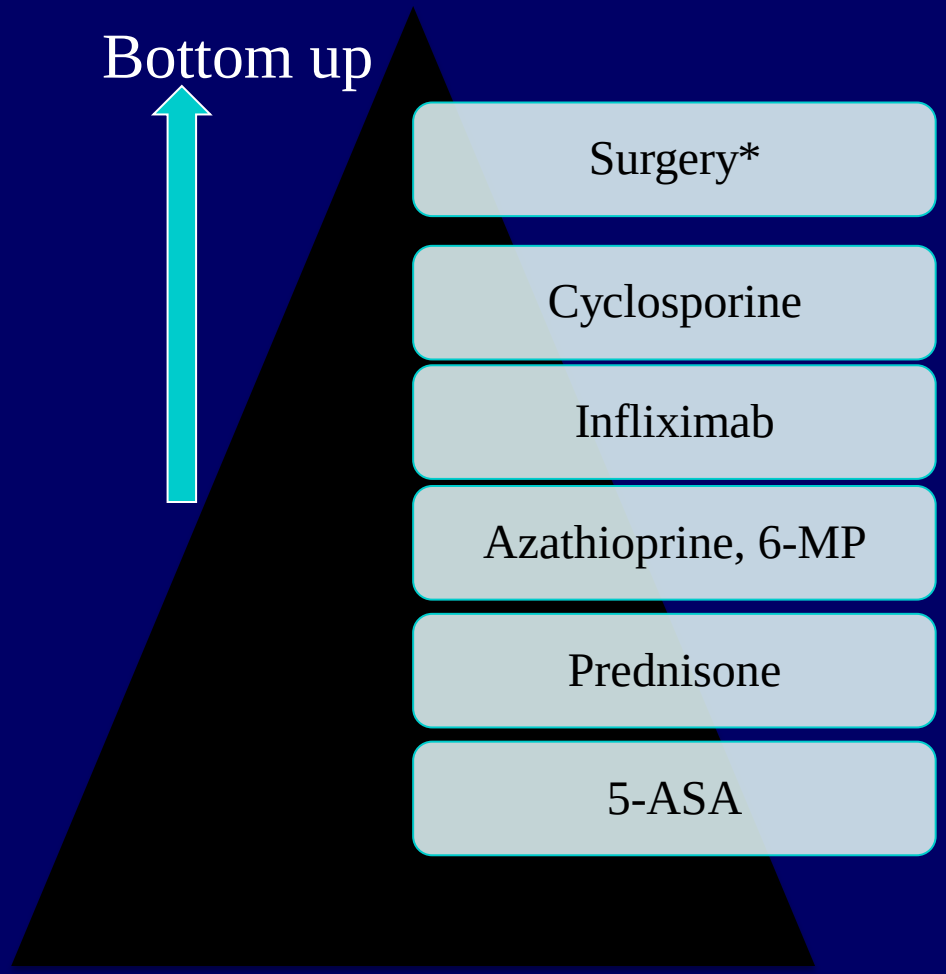
Ulcerative colitis



Medications with Proven Efficacy in Crohn's Disease and Ulcerative Colitis

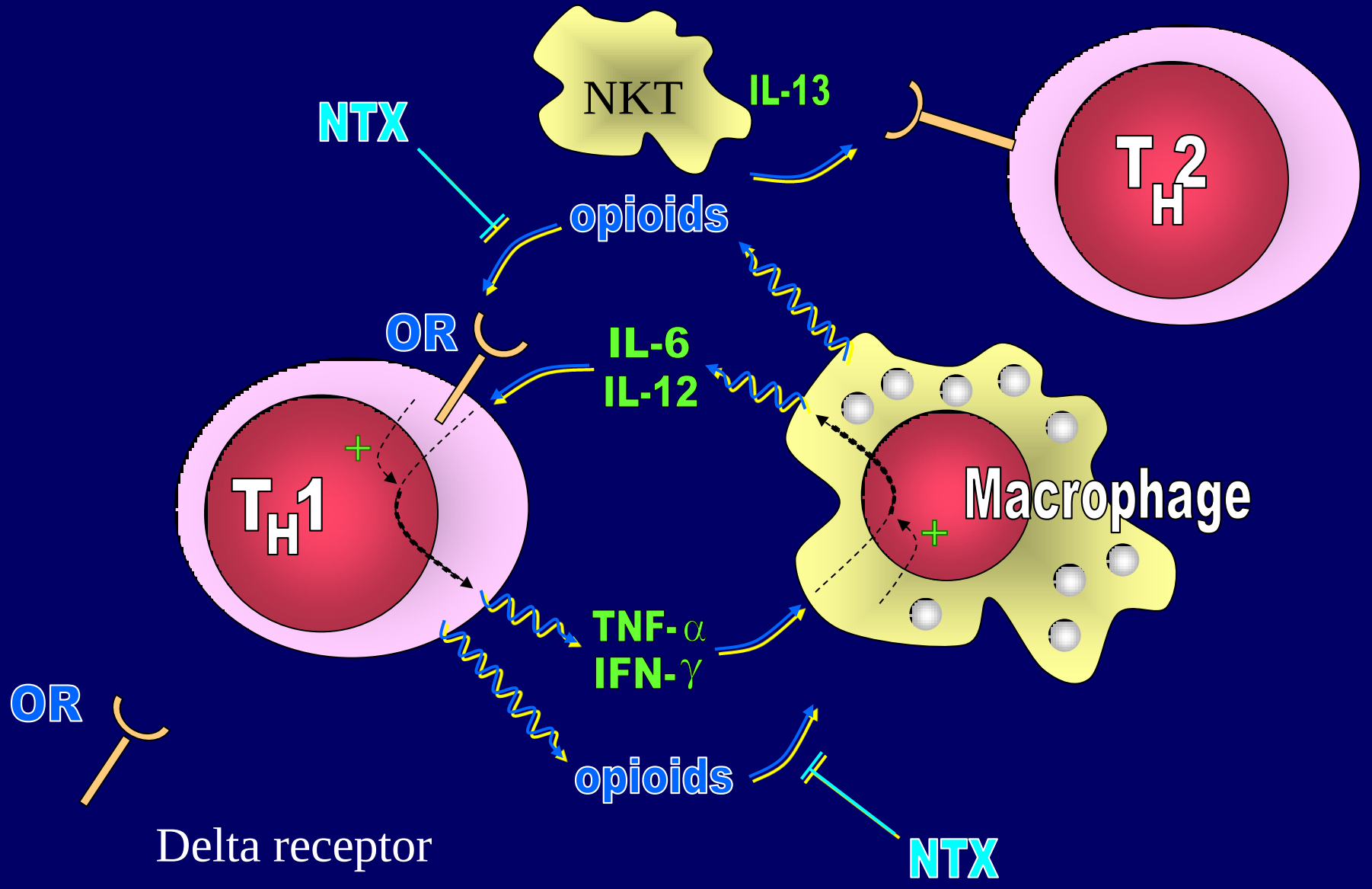


Crohn's disease

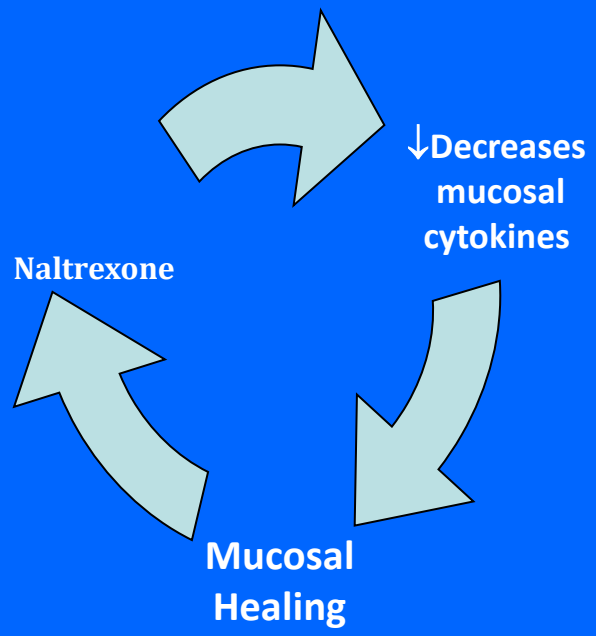


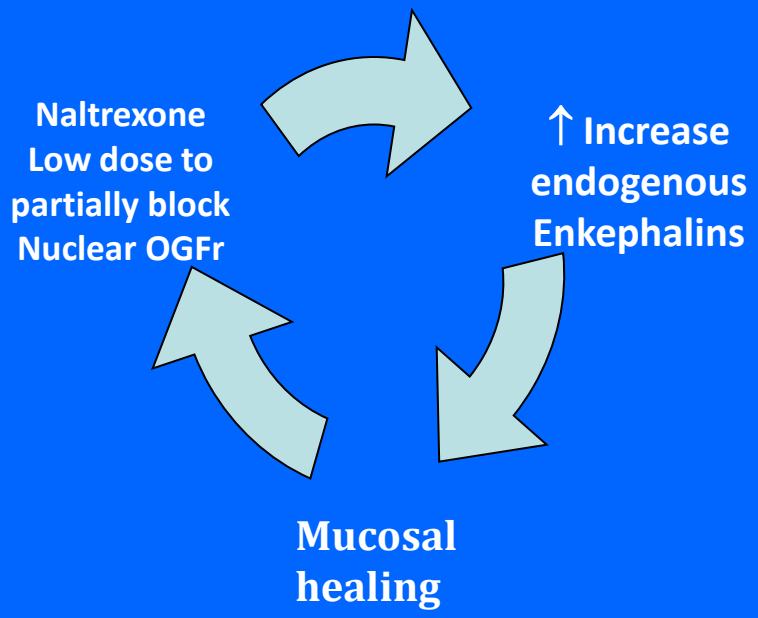
Ulcerative colitis

Model: Opioids, Naltrexone and the Inflammatory State



Mechanism of Action?





Blocked Cytokines
Delta Opioid Receptor

Increased enkephalins
OGF receptor

Effects of Naltrexone on IBD Animal Studies

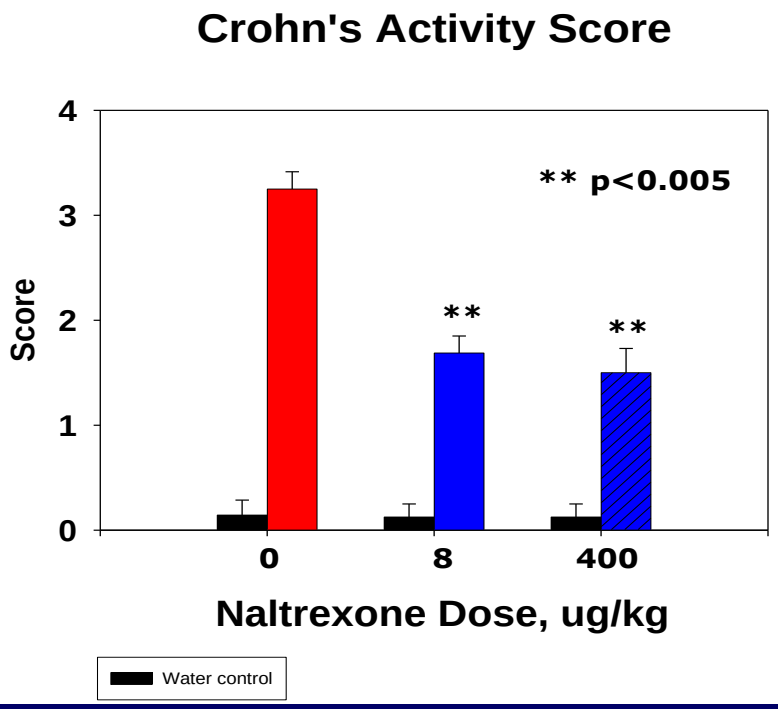
Animal Models IBD:
DSS, TNBS, Oxazolone
IL-10 KO mouse

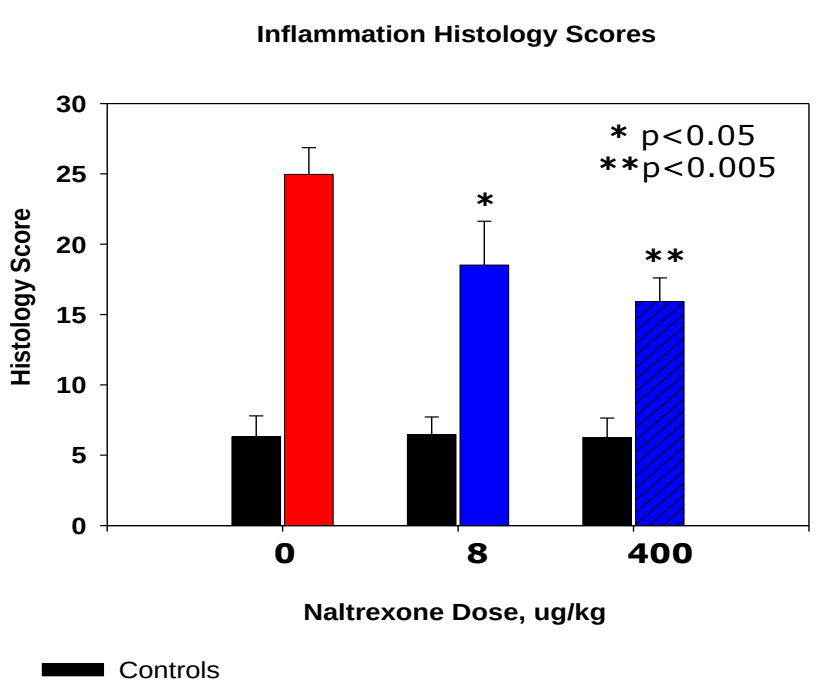
Purpose of study:

To test the effects of various doses of the opioid antagonist naltrexone on reversing active colitis in an animal model.

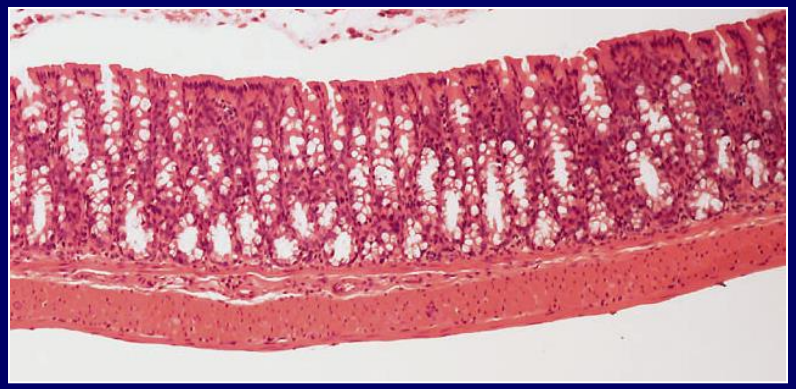
J.Immunotoxicol., 5: 179-187, 2008.

Low-dose Naltrexone Improves Activity & Histology Scores

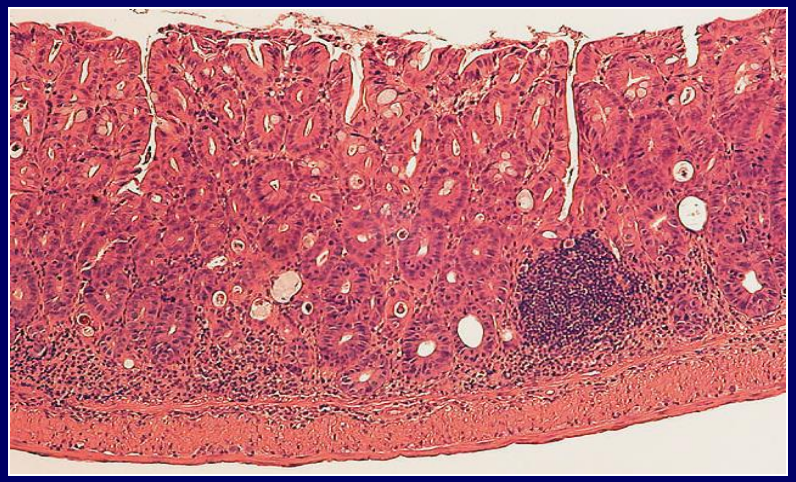




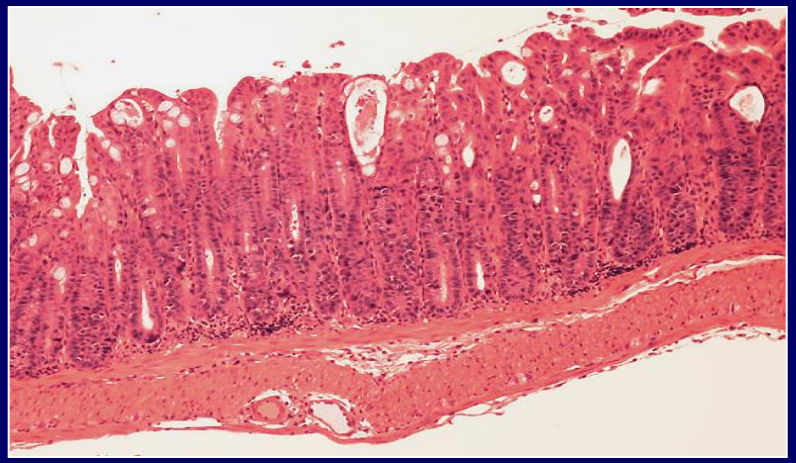
Histology: Colonic Inflammation is Reduced by Low-Dose Naltrexone



No DSS + Saline, Control

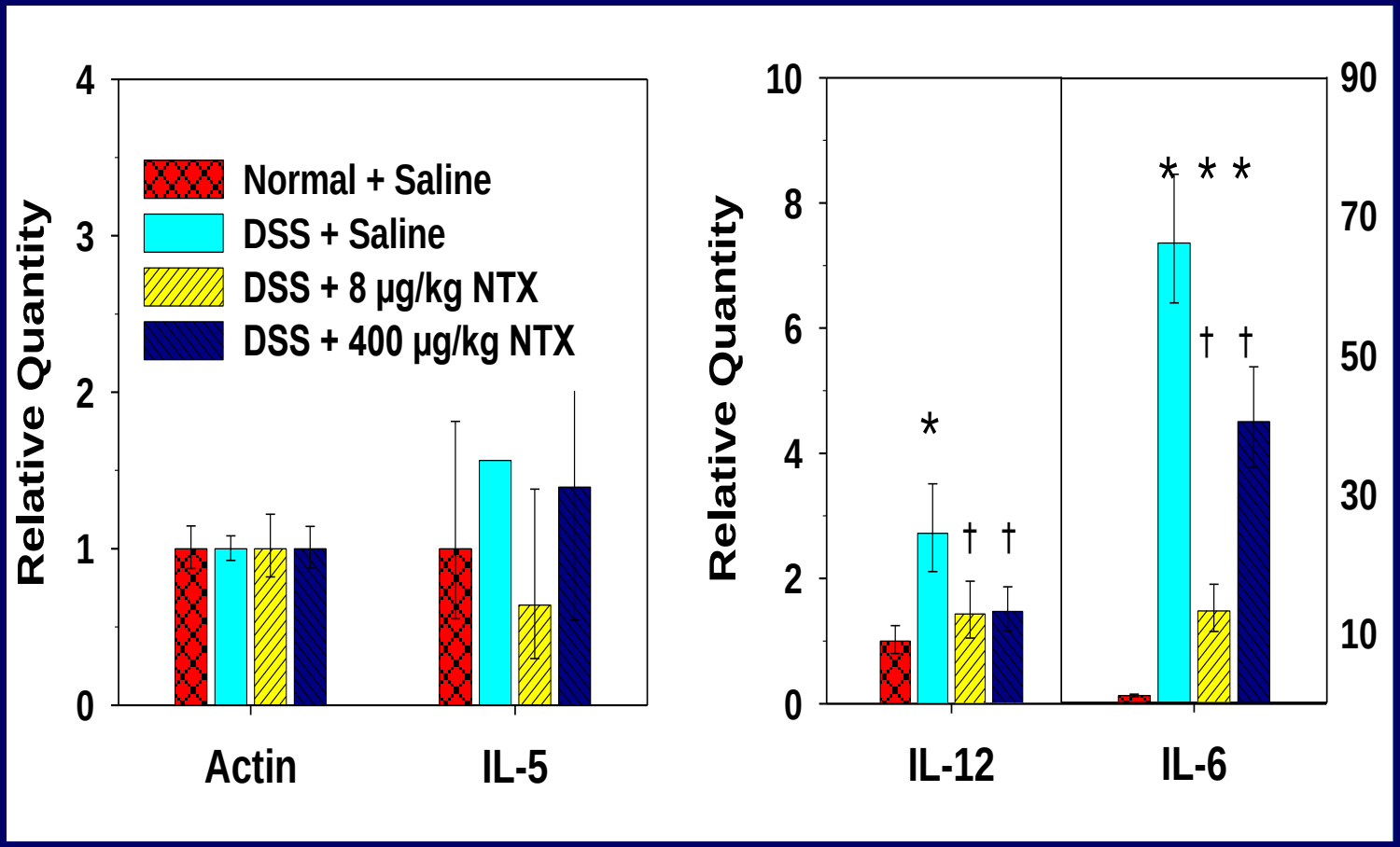


DSS Colitis + Saline Control



DSS colitis + Naltrexone

Low-dose Naltrexone decreases pro-inflammatory cytokines in IBD



Human Studies: Pilot Study

Smith et al. American Journal of Gastroenterology 2007; 102:820-828.

Study Design

- Phase 2 prospective open-labeled feasibility study

- Purpose: to test the safety and toxicity and efficacy of naltrexone 4.5 mg/d in subjects with active Crohn's disease

Parameters of Measurement

CDAI scores

1. **Response = decrease by 70/ 100 points**
2. **Remission = Score of 150 or less**

Laboratory indices (CRP, ESR, CBC, chemistries)

Quality of Life Surveys:

1. **IBD questionnaire**
2. **SF-36 Survey**

Criteria for selection

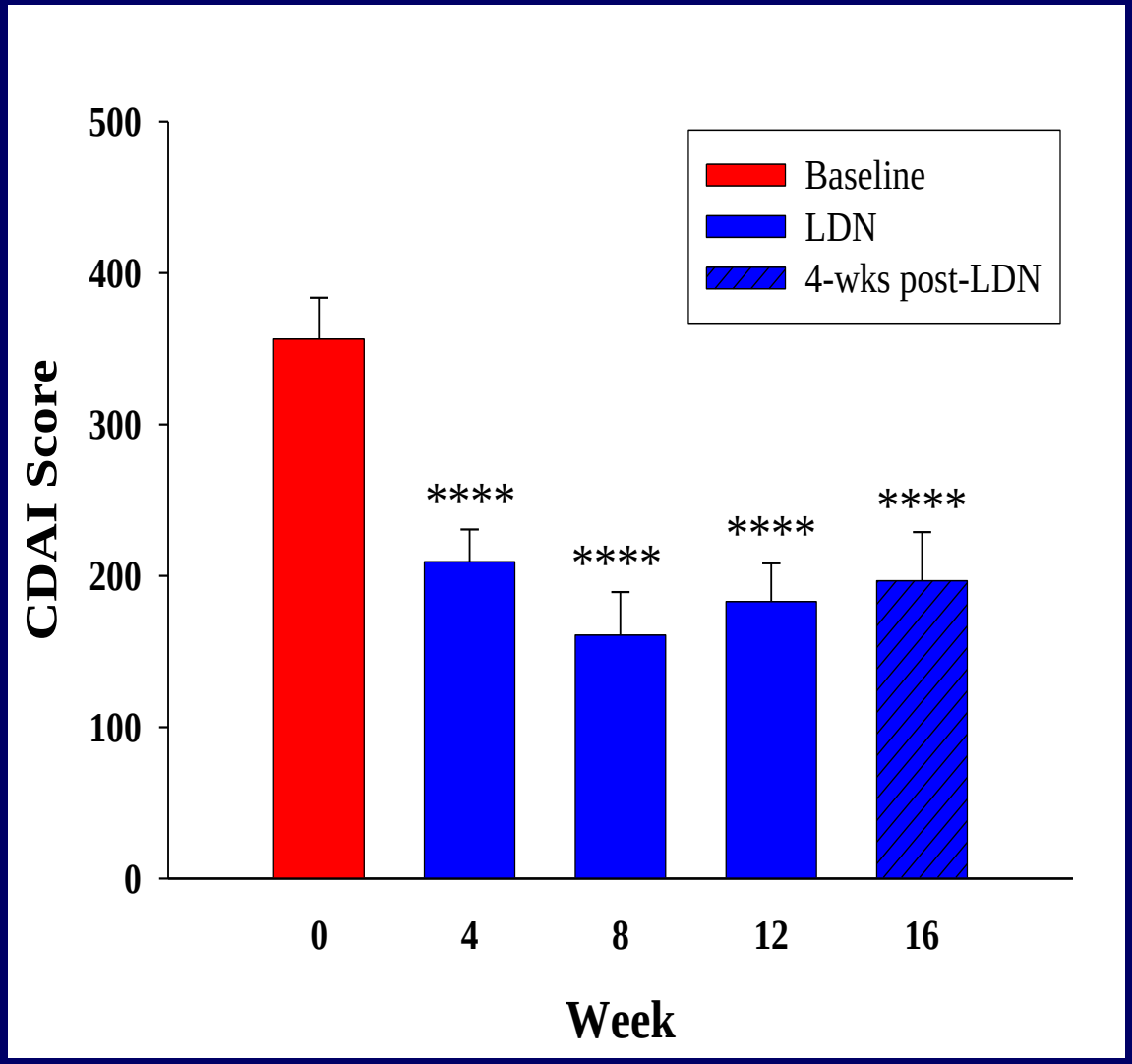
Inclusion

- 18 yrs and older
- CDAI score ≥220
- Stable medications
- No serious medical illnesses

Exclusion

- Anti-TNF biologics
- Ostomies
- Pregnancy
- Abnormal liver enzymes

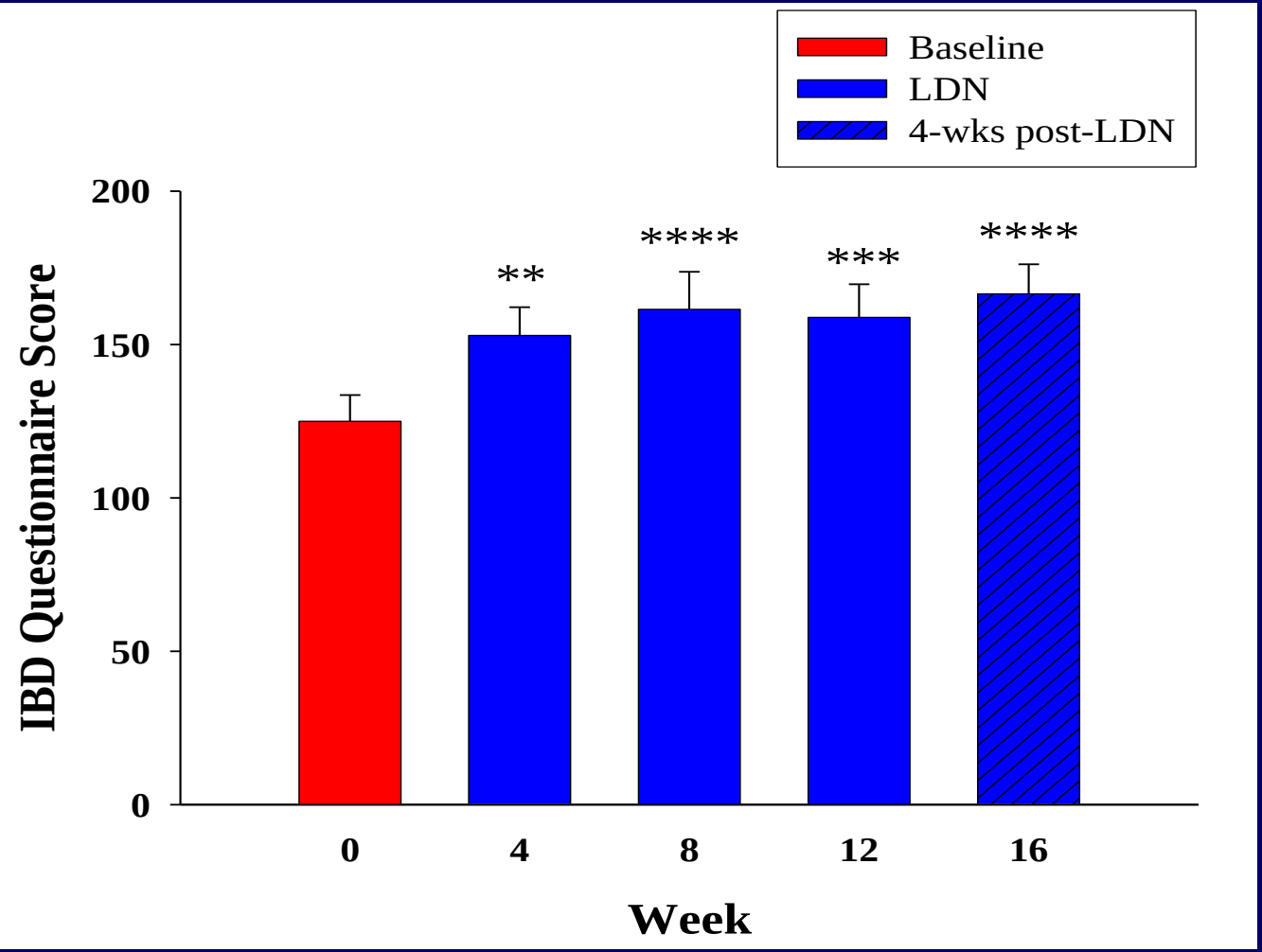
CDAI Scores Improve with Naltrexone



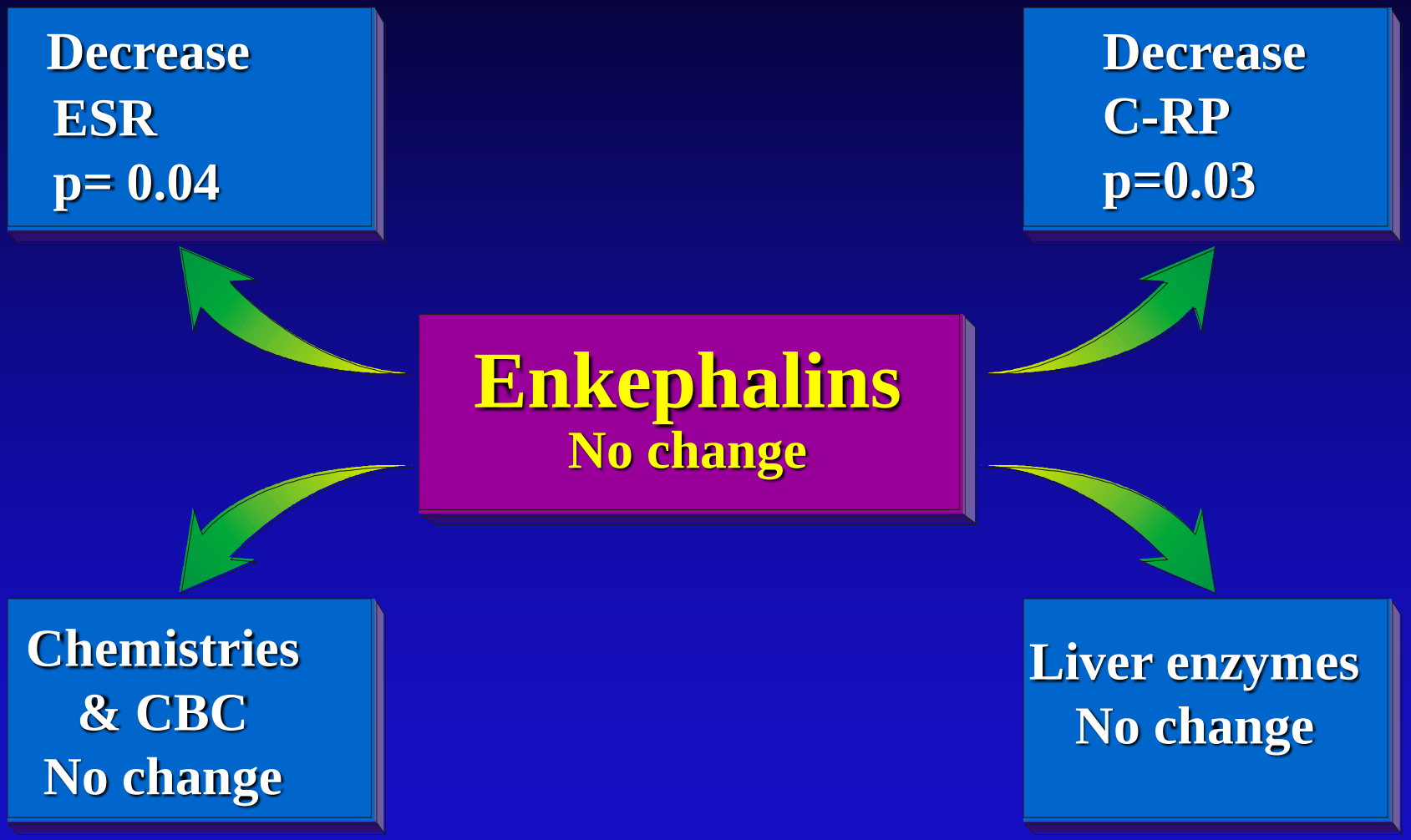
- 17 subjects completed the pilot study
- 2 subjects with open fistulas had closure
- Over 80% had improvement in CDAI score
- 30-40% remission

Improved Quality of Life with Naltrexone

IBDQ



Results of Blood Tests



Summary of Pilot Human Study

- **Low Dose Naltrexone therapy:**
  - **Improved CDAI scores**
  - **Improved Quality of Life**
  - **Increased chance of remission**
  - **Decreased blood inflammatory markers**
  - **Had minimal side effects**

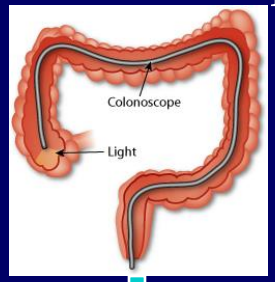
Problems: Open labeled, small numbers, no endoscopic evaluation

Phase 2 placebo controlled double blind study trial

Screen → **Labs, CDAI**

C-RP & Location

Randomize Colonoscopy



BLINDED

4.5 mg Naltrexone

Placebo

3 months Monthly visits

CDEIS & biopsies

Repeat Colonoscopy

3 months Monthly visits

Open-labeled

4.5 mg Naltrexone

Repeat Colonoscopy

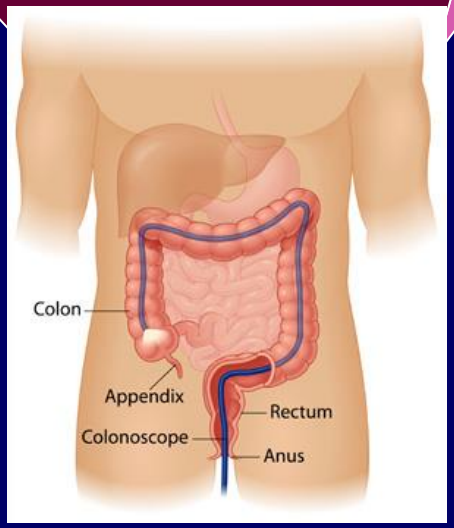
Naltrexone

Parameters of Measurement

CDAI scores

Primary Outcome: Decline in CDAI score

Laboratory
Safety monitoring



Endoscopy scores
Mucosal healing

Quality of Life Surveys
IBDQ, SF-36

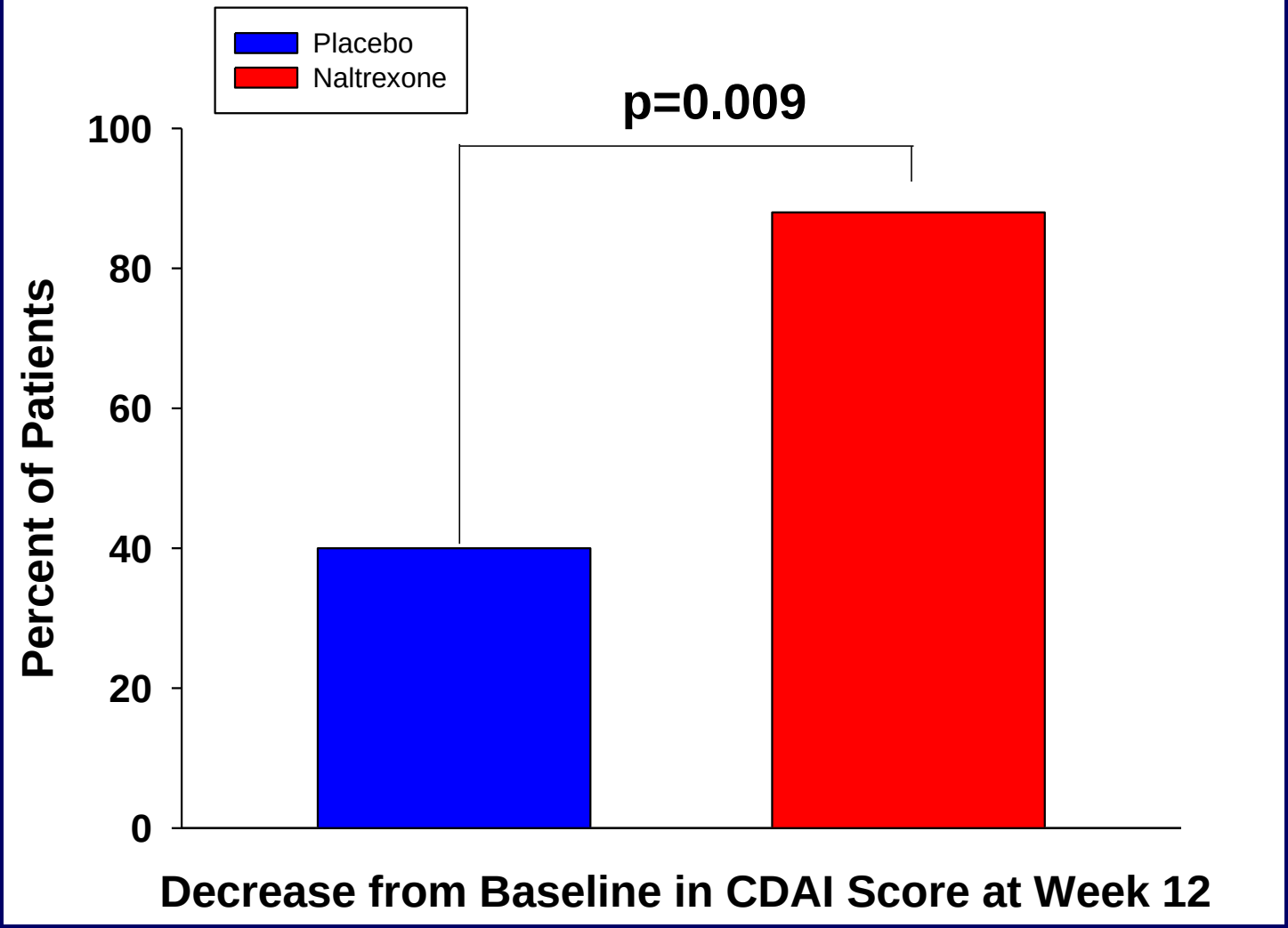
Histology Inflammatory scores

Secondary Outcome: Mucosal healing

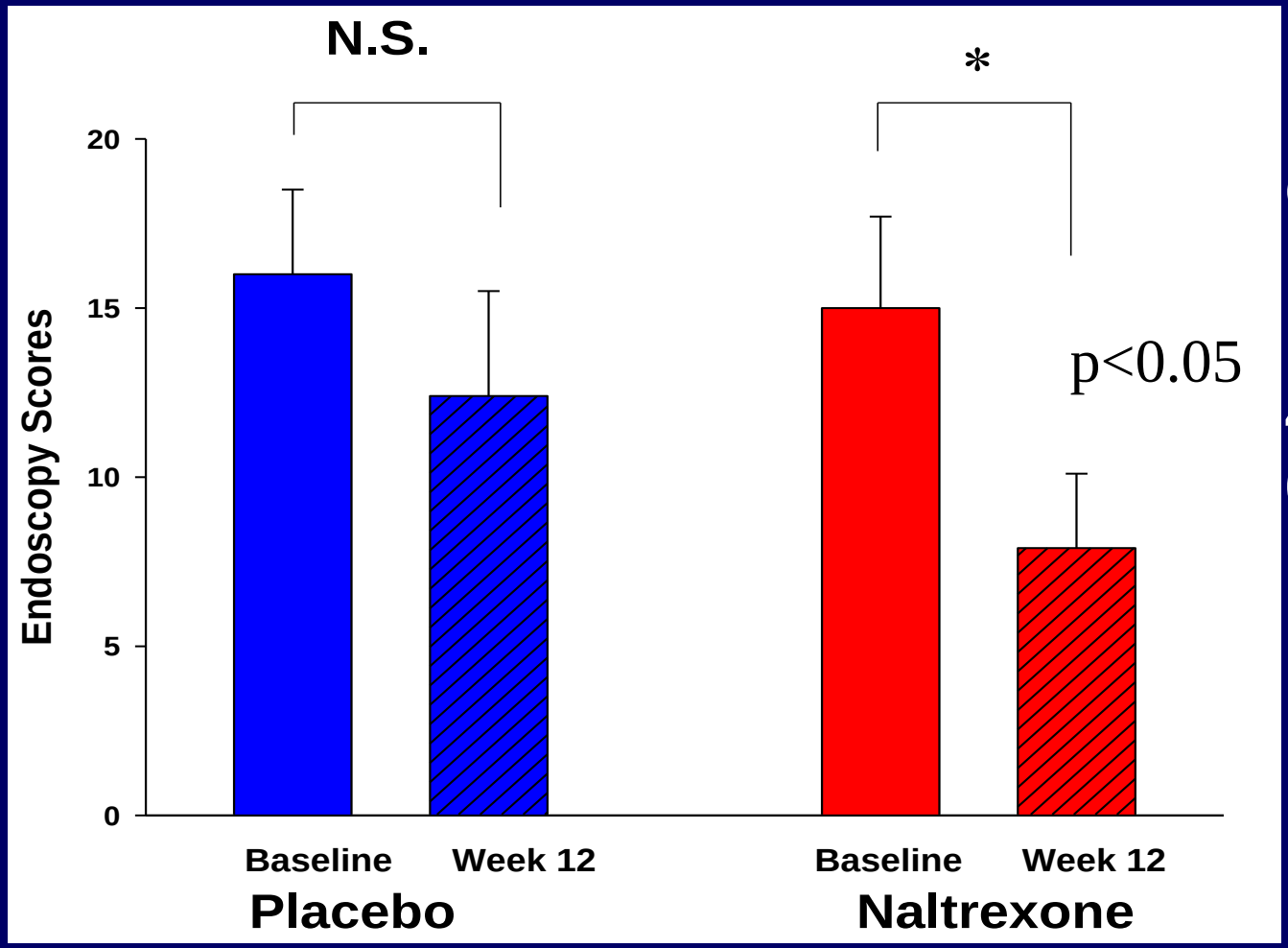
Table 1. Patient Demographics and Disease Characteristics

Treatment group parameter	Placebo	Naltrexone	p value
Age (years); mean ± S.E.M. (Range)	44.8 ± 2.8 (26-67)	40.5 ± 2.4 (21-60)	1.0
Gender, (% of males)	37.5	35.3	1.0
(% females)	62.5	64.7	1.0
Prior anti-TNFα treatment %	56	61	1.0
Concomitant medications for Crohn's (% of patients)			
Aminosalicylates	44	56	0.73
Immunomodulators	31	6	0.08
Corticosteroids	19	28	0.70
Antibiotics	6	6	1.0
None	38	17	0.25
Location of Disease (%)			
Small bowel only	38	34	1.0
Ileocolic	44	55	1.0
Colon	13	6	0.59
Baseline CDAI (mean± SEM)	327 ± 19	365 ± 16	0.13
Baseline IBDQ (mean± SEM)	136 ± 5.8	121 ± 6.1	0.08
Baseline SF36 (mean± SEM)	44.5 ± 3.9	35.9 ± 4.6	0.16
Baseline CRP mg/dl (mean ± SEM)	1.19 ± 0.3	1.55 ± 0.3	0.41
Baseline ESR mm/hr (mean ± SEM)	33.5 ± 6.3	26.6 ± 5.7	0.45

Primary Outcome Clinical Response CDAI Scores



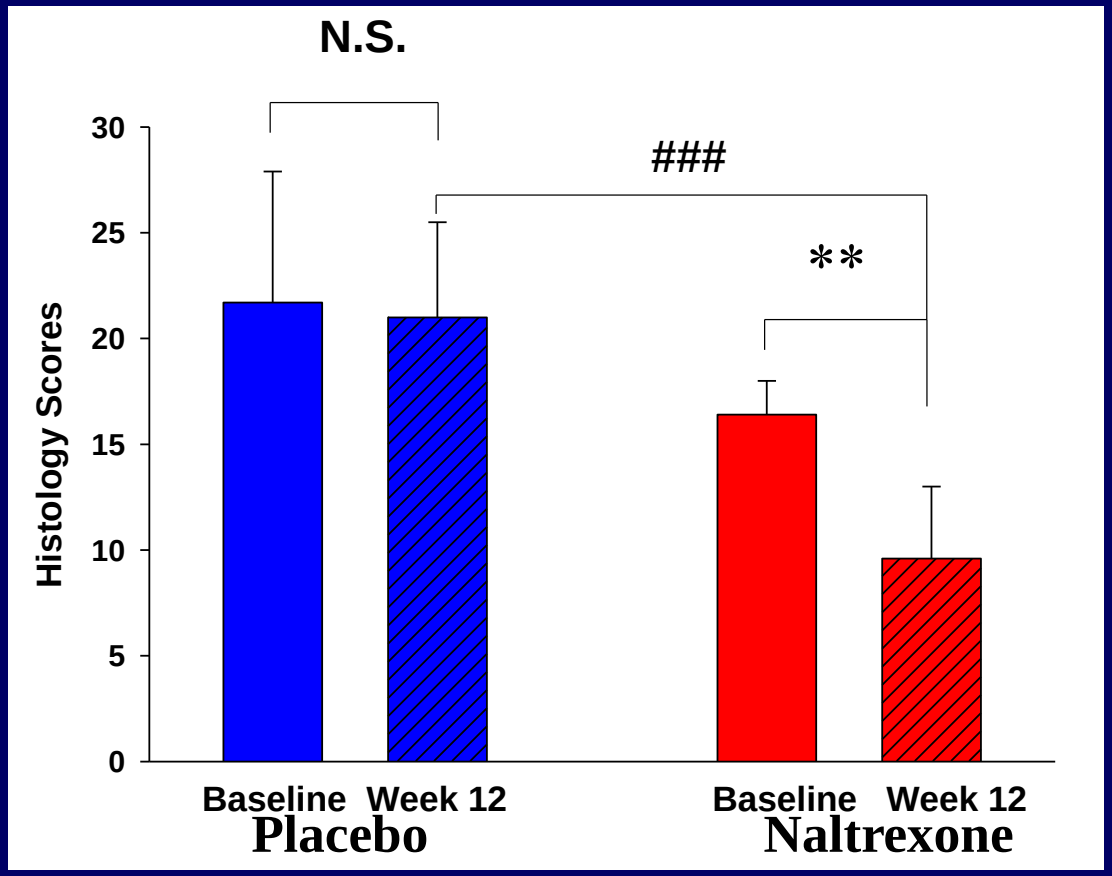
Endoscopic Colonoscopy Scores



CDEIS <6 Endoscopic Remission: 44% Naltrexone 0% on Placebo

Validated Endoscopy scoring system.
Mary, J. Y. and Modigliani, R Gut, *30*: 983-989, 1989.

Histologic Inflammation Scores



**Significantly different from baseline at p<0.05

significantly different from placebo treated controls at p<0.0001

Validated Crohn's Histology scoring system.
Dieleman, L., Clin.Exp.Immunol., *114*: 385-391, 1998.

Naltrexone treated

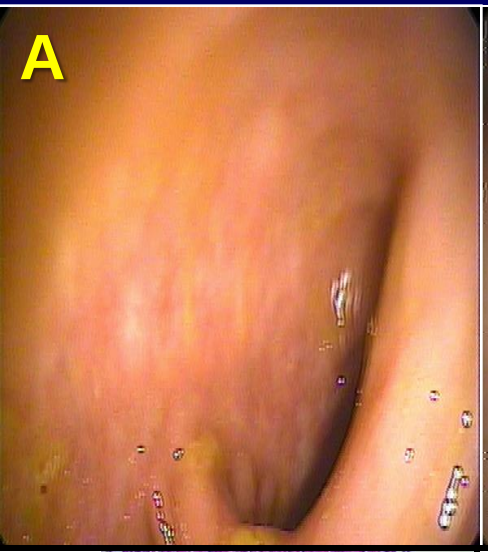
Placebo treated

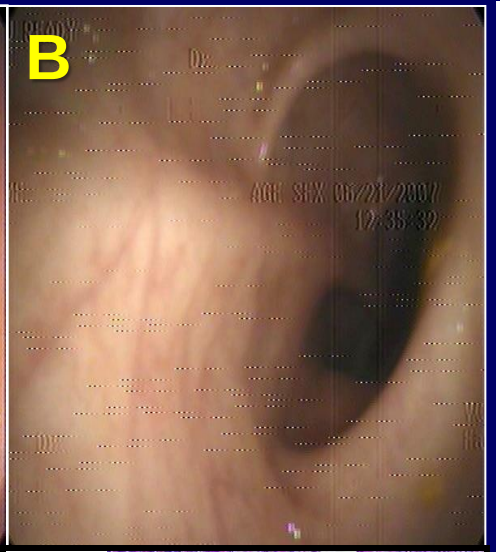
Baseline

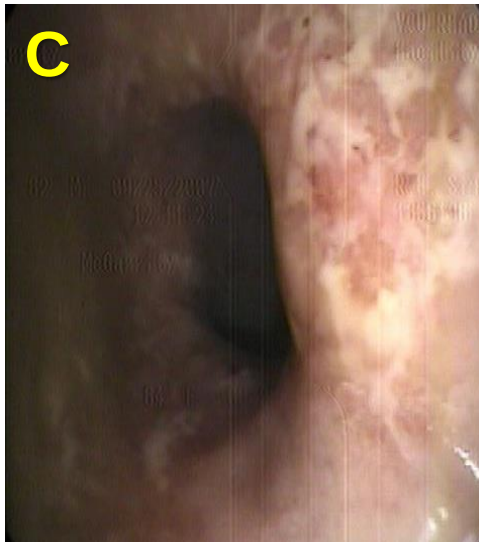
Week 12

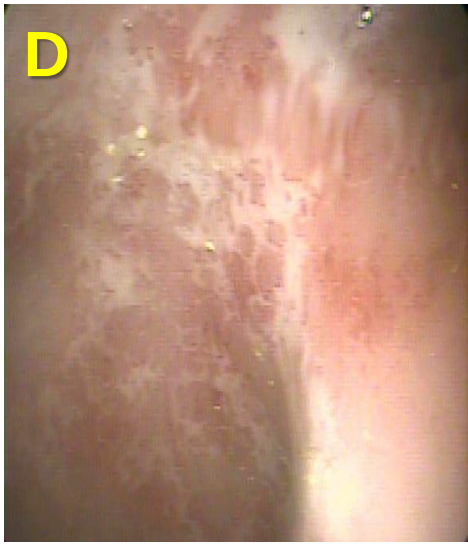
Baseline

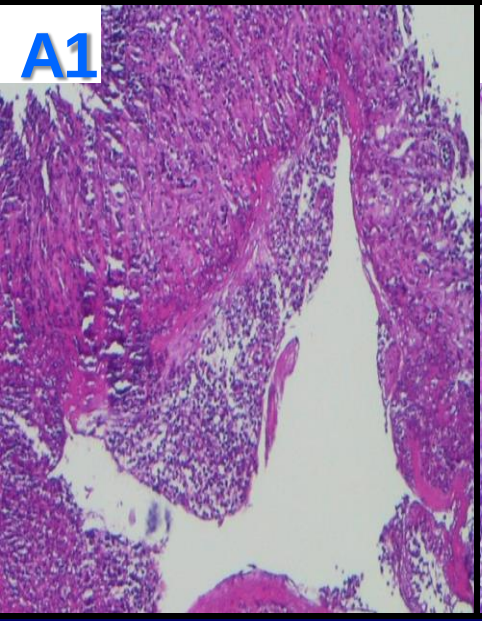
Week 12

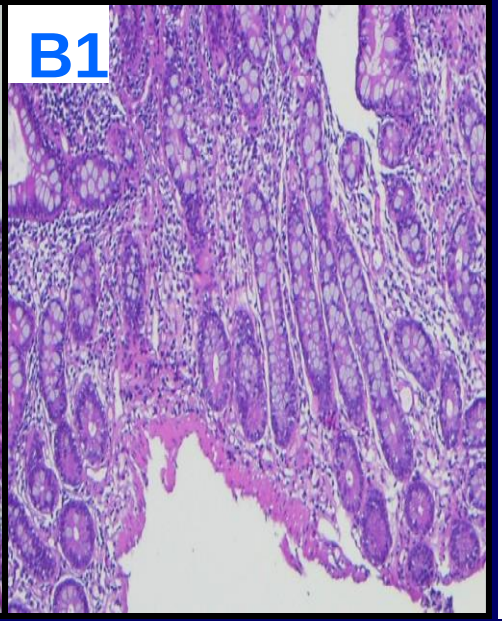


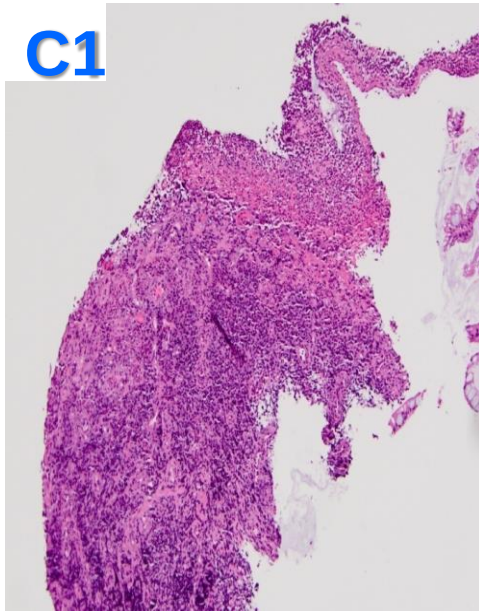


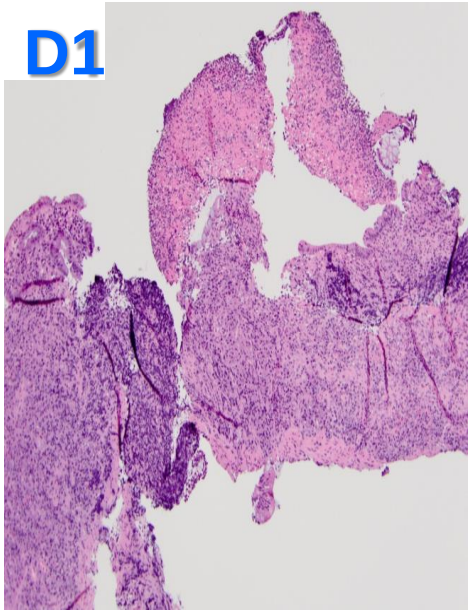












Side Effects

Side Effect /Symptom	Placebo	Naltrexone	p-value
Insomnia	5	5	0.3
Unusual dreams	3	2	0.3
Headache	2	4	1.0
Flatulence	5	6	0.5
Loss of appetite	0	2	0.6
Vomiting	1	3	1.0
Diarrhea	5	7	0.7
Abdominal pain	5	5	0.3
Nausea	4	4	0.5
Hair loss	1	0	1.0
Fatigue	3	0	0.04*
Constipation	0	2	0.6
Hair growth	0	1	1.0

Safety & Toxicity

Placebo treated subject was Unblinded and treated with Naltrexone and responded.

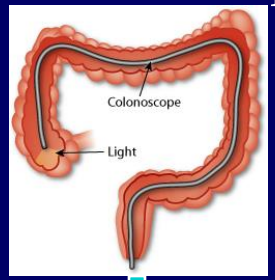
- Two subjects had flare-up in symptoms on study: 1 on naltrexone and 1 on placebo.
- One subject with Reflex sympathetic dystrophy had worsening of her neurogenic pain on naltrexone.
- Two subjects on naltrexone had transient elevation in liver transaminases.

Phase 2 placebo controlled double blind study trial

Screen → **Labs, CDAI**

C-RP & Location

Randomize Colonoscopy



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Open-labeled

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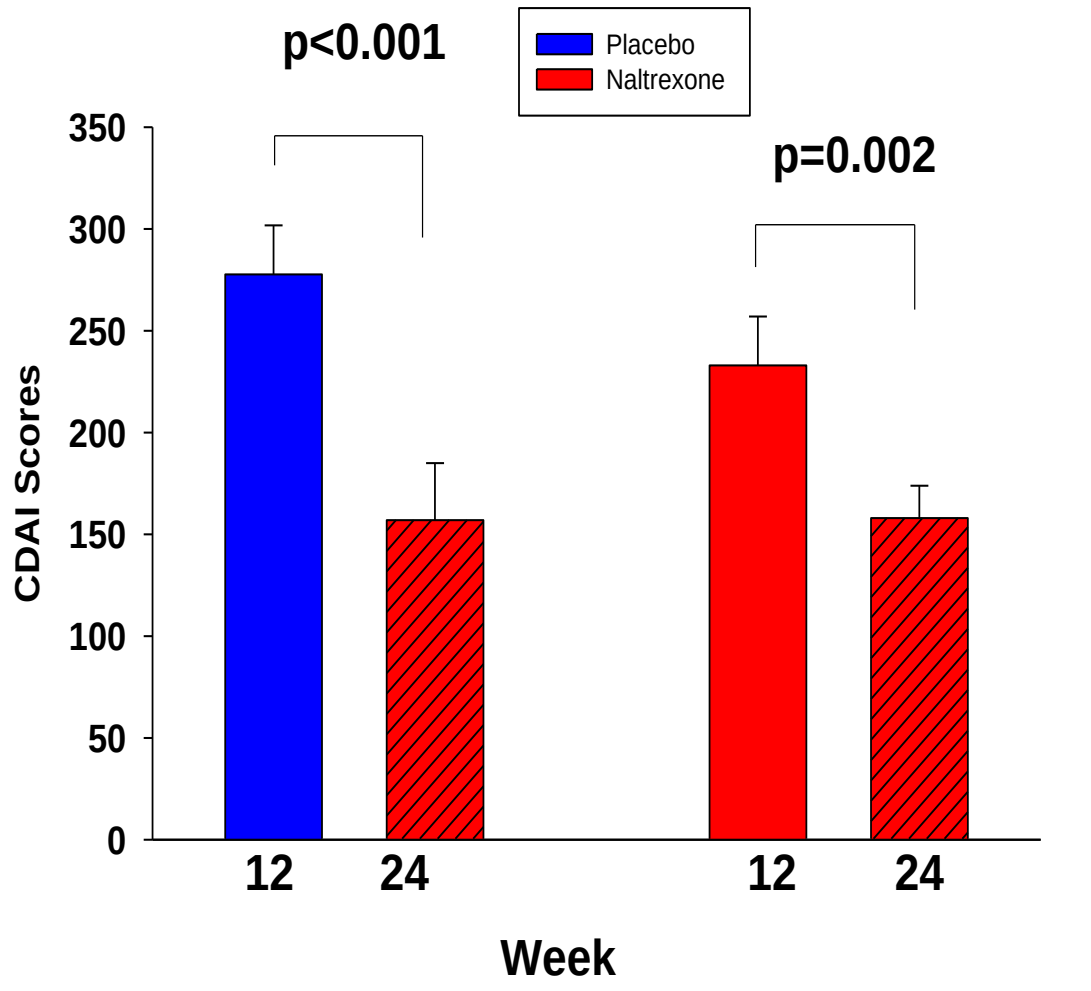
Naltrexone

Repeat Colonoscopy

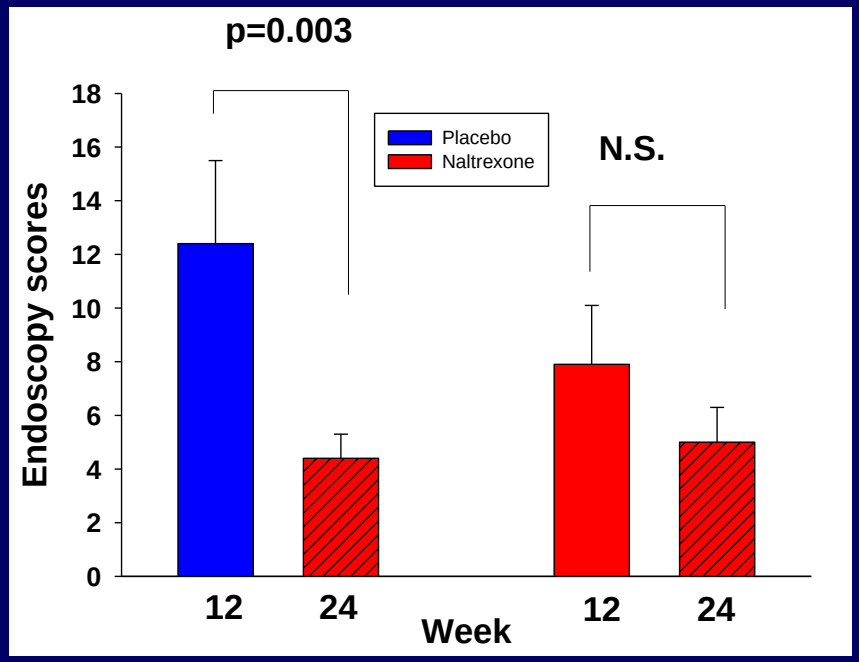
Naltrexone

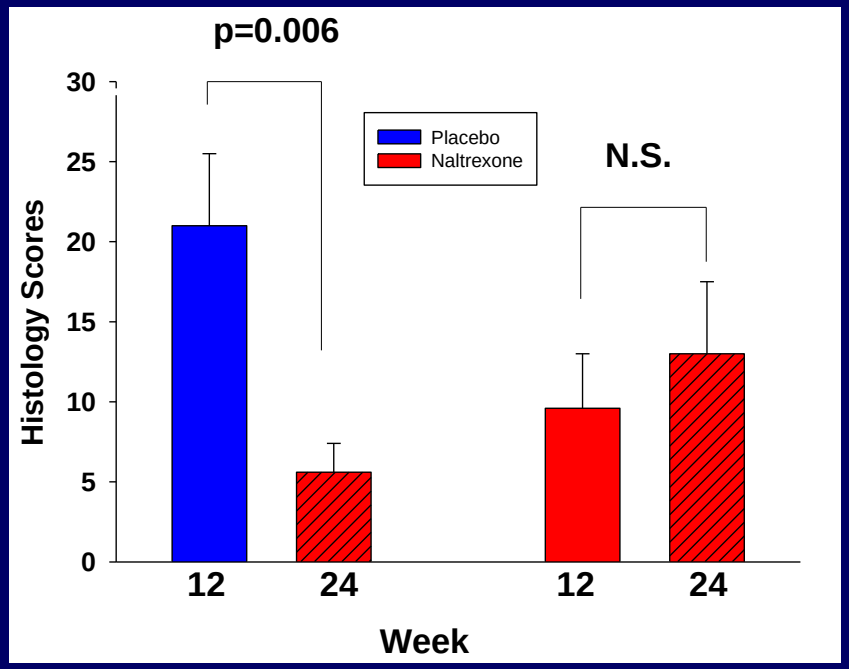
Extended Open-labeled study CDAI scores up to 24 wks



Remission achieved CDAI Score <150 With Naltrexone : 30% after 12 weeks 50% after 24 weeks

Extended Open-labeled study colonoscopy scores





Endoscopy Scores

Histology Scores

So if mucosal healing occurs, it will do so by week 12

Plasma Cytokines Decreased

- Pretreatment

INF-γ = 32.76 pg/ml

TNF-α = 4.39 pg/ml

- Post-treatment

INF-γ = 14.83 pg/ml

TNF-α = 1.77 pg/ml

Enkephalin Plasma levels: No statistical change

Summary of Adult Clinical Trials

- Oral naltrexone improves clinical activity, chance of remmission, and induces mucosal healing compared to placebo controls
- If mucosal healing occurs, it does so by week 12
- The mechanism of action appears to be related to the lowering of inflammatory cytokines
- Remission rate equal or exceed that for biologics
- Side effects are minimal

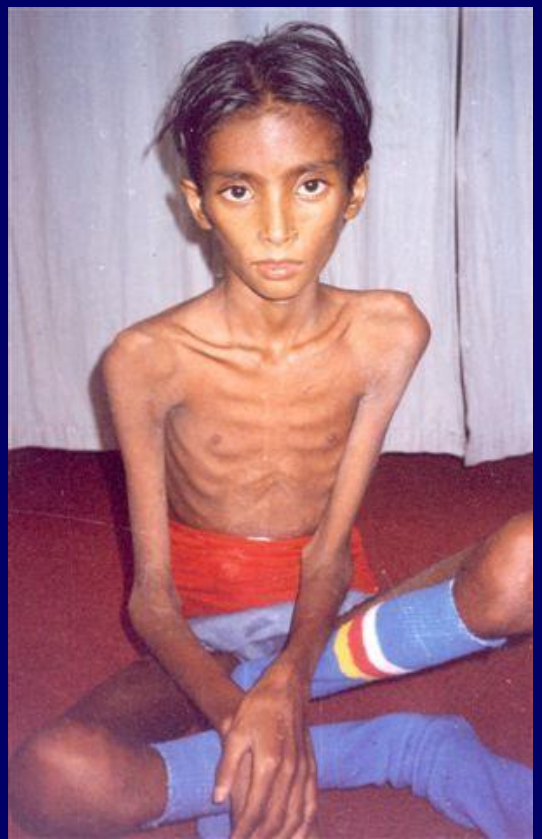
Digestive Diseases & Science (2011) 56:2088–2097

Crohn's Disease in Children

(J Clin Gastroenterol 2013;47:339–345)

Children with Crohn's disease exhibit a unique set of complications such as:

- growth failure
- school absence
- Malnutrition
- Depression



Thank you to Mr. F. Bell
Given-Share Sponsor

Crohn's Disease in Children

Medications used for Crohn's have increased risks in children including:

- Infections
- Growth retardation
- Malignancies: leukemias, hepatosplenic lymphoma

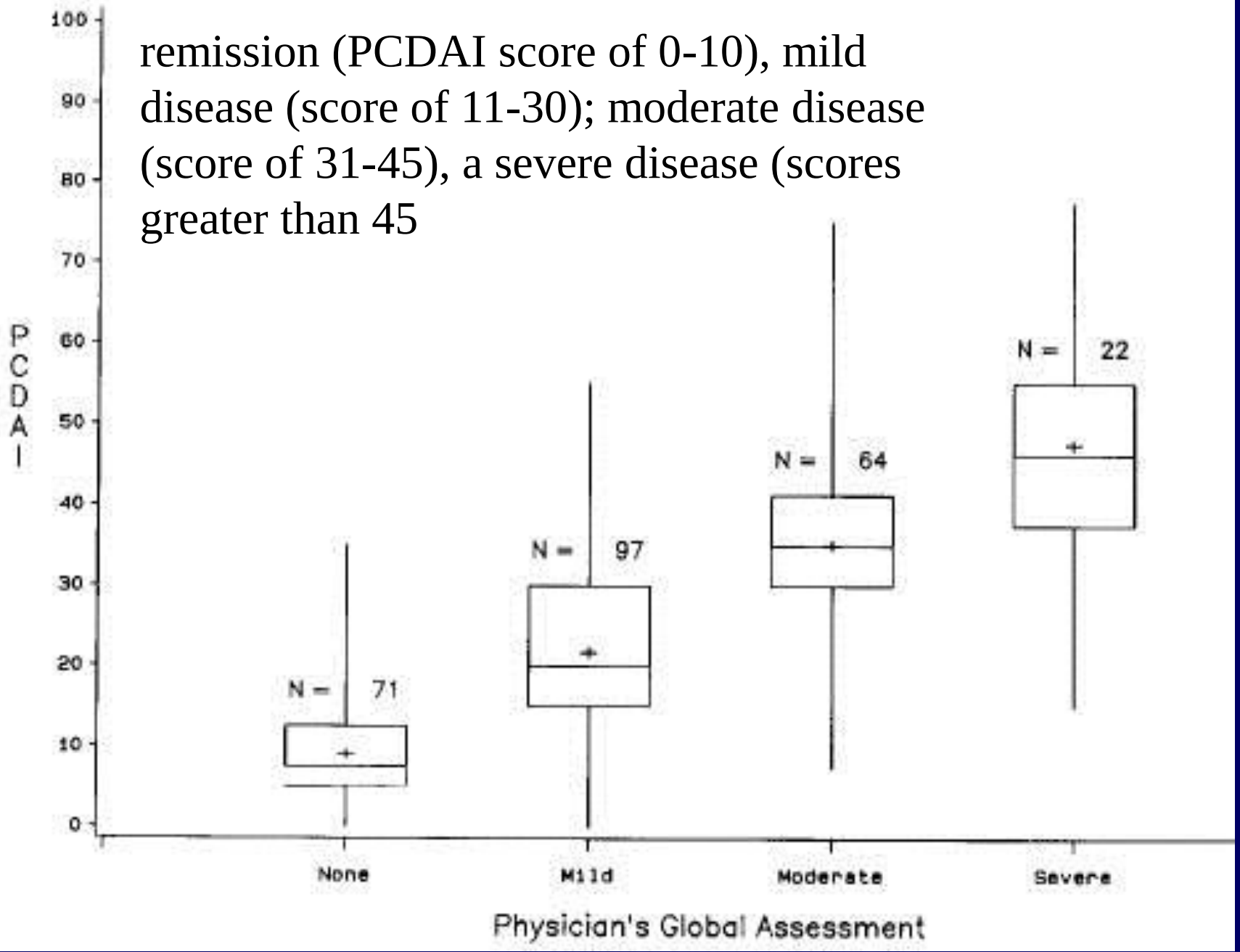
** FDA black box warning on anti-TNFα

Hypothesis

Aim: Evaluate the ability of naltrexone to reverse the inflammatory activity in children with moderate to severe Crohn's disease compared to baseline values & placebo treated controls.

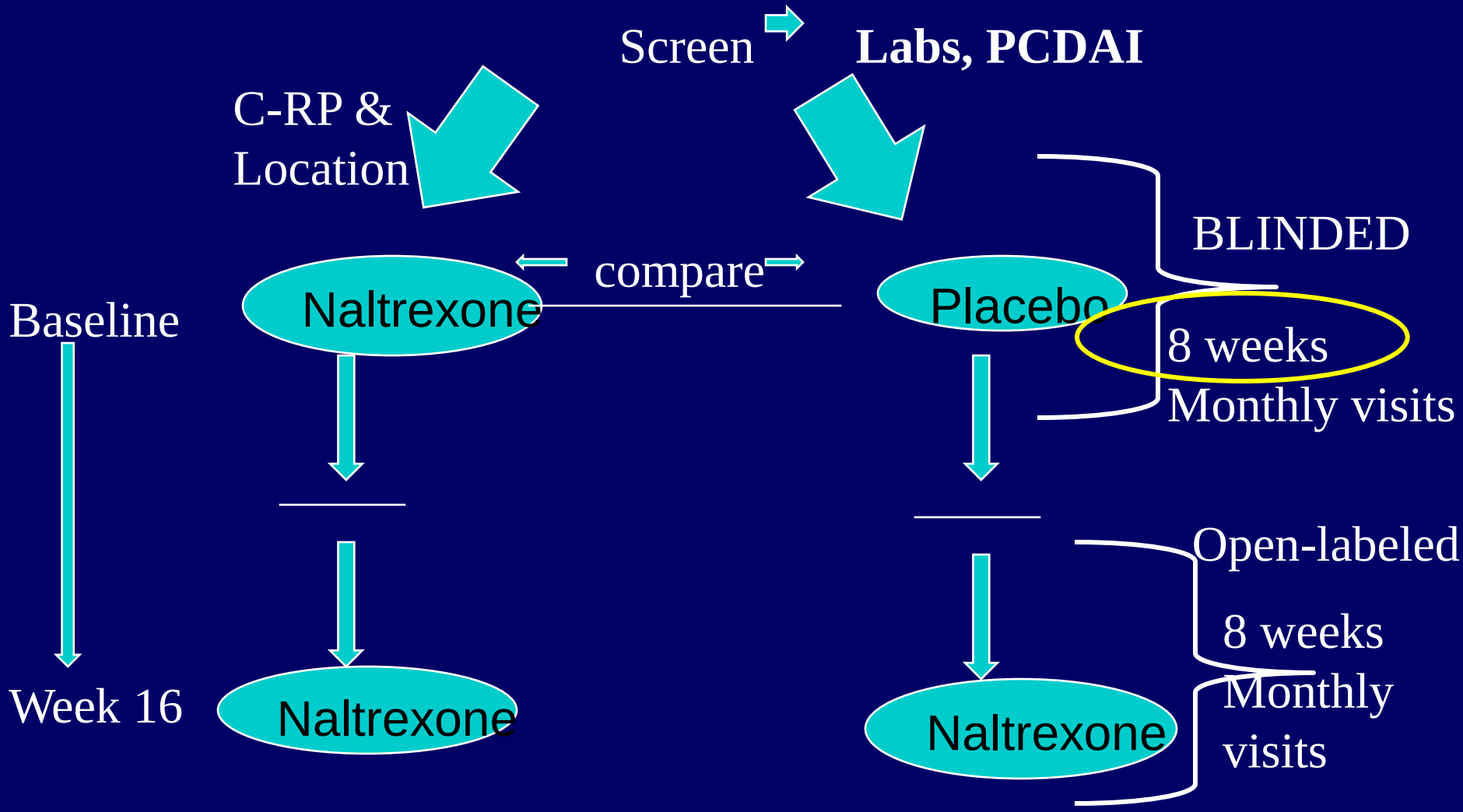
Sponsor: Given-Share Foundation

remission (PCDAI score of 0-10), mild disease (score of 11-30); moderate disease (score of 31-45), a severe disease (scores greater than 45



STUDY DESIGN

Investigator initiated, translational
prospective, double-blind, placebo-controlled



Criteria for selection

Inclusion

- Ages 6-17 yrs
- PCDAI score ≥30
- Stable medications
- No serious medical illnesses

Exclusion

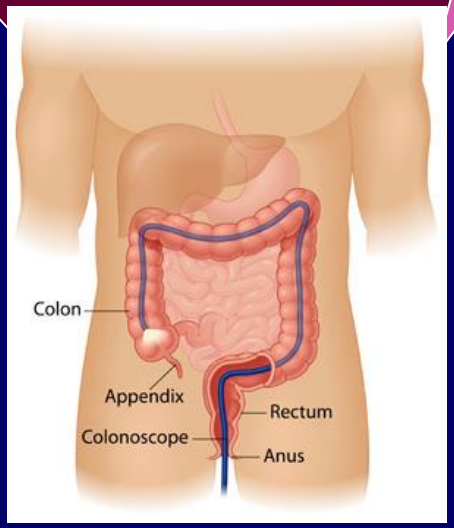
- Anti-TNF biologics
- Ostomies
- Pregnancy
- Abnormal liver enzymes
- Steroids > 10 mg/d

Parameters of Measurement

***Primary Outcome

PCDAI scores *

Laboratory
Safety monitoring



Growth: Height & Weight

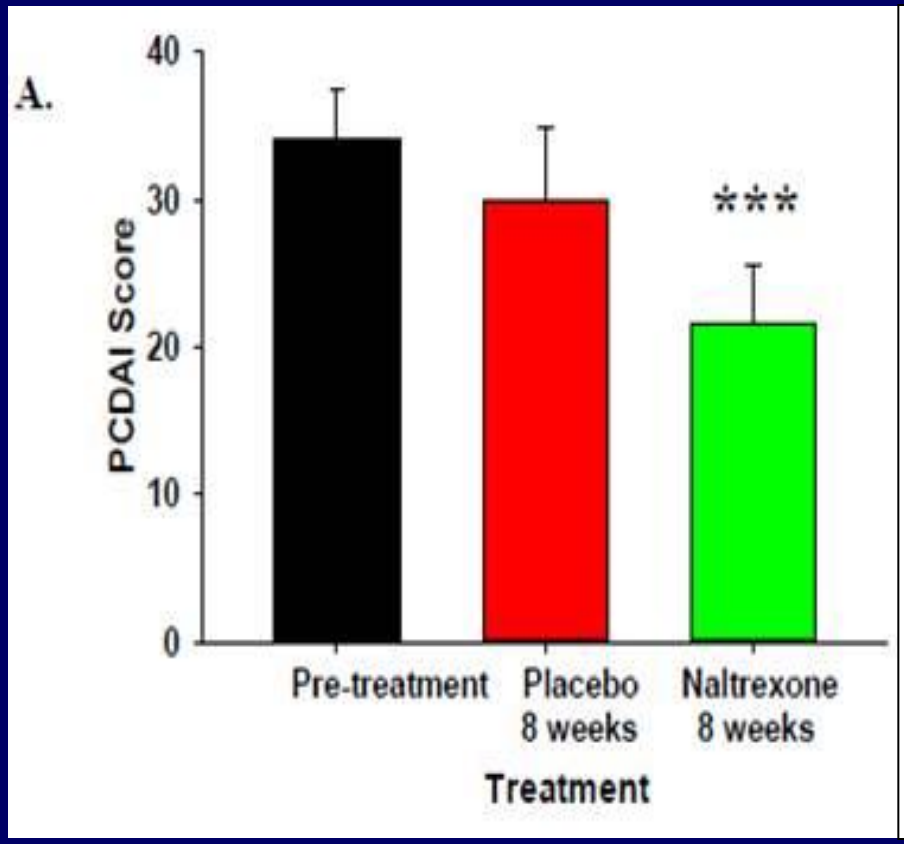
Quality of Life Survey
Impact III

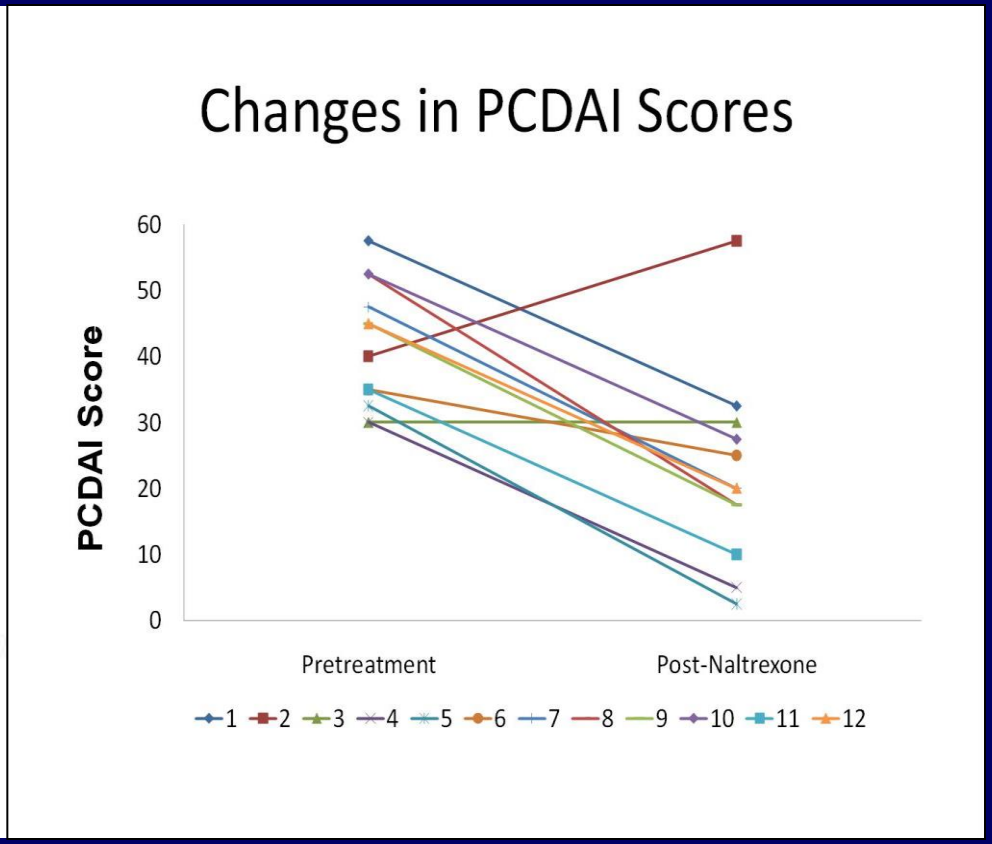
Harvey-Bradshaw Index

Patient Demographics

Characteristics	N=14 (2 screen failures)
Age (years); mean ± S.E.M. (Range)	12.4 ± 0.8 years (8-17, range)
Gender, N (% of patients)	Males 5 (37.5) Females 9 (62.5)
Body weight (kg); mean ± S.E.M.	Males 37.4± 3.3 Females 45.9 ± 5.2
Prior anti-TNFα therapy	17%
Concomitant meds for Crohn's (% of patients)	Aminosalicylates (67%) Immunomodulators (thiopurines) (75%) Corticosteroids (25%) Antibiotics (17%)

Clinical Response





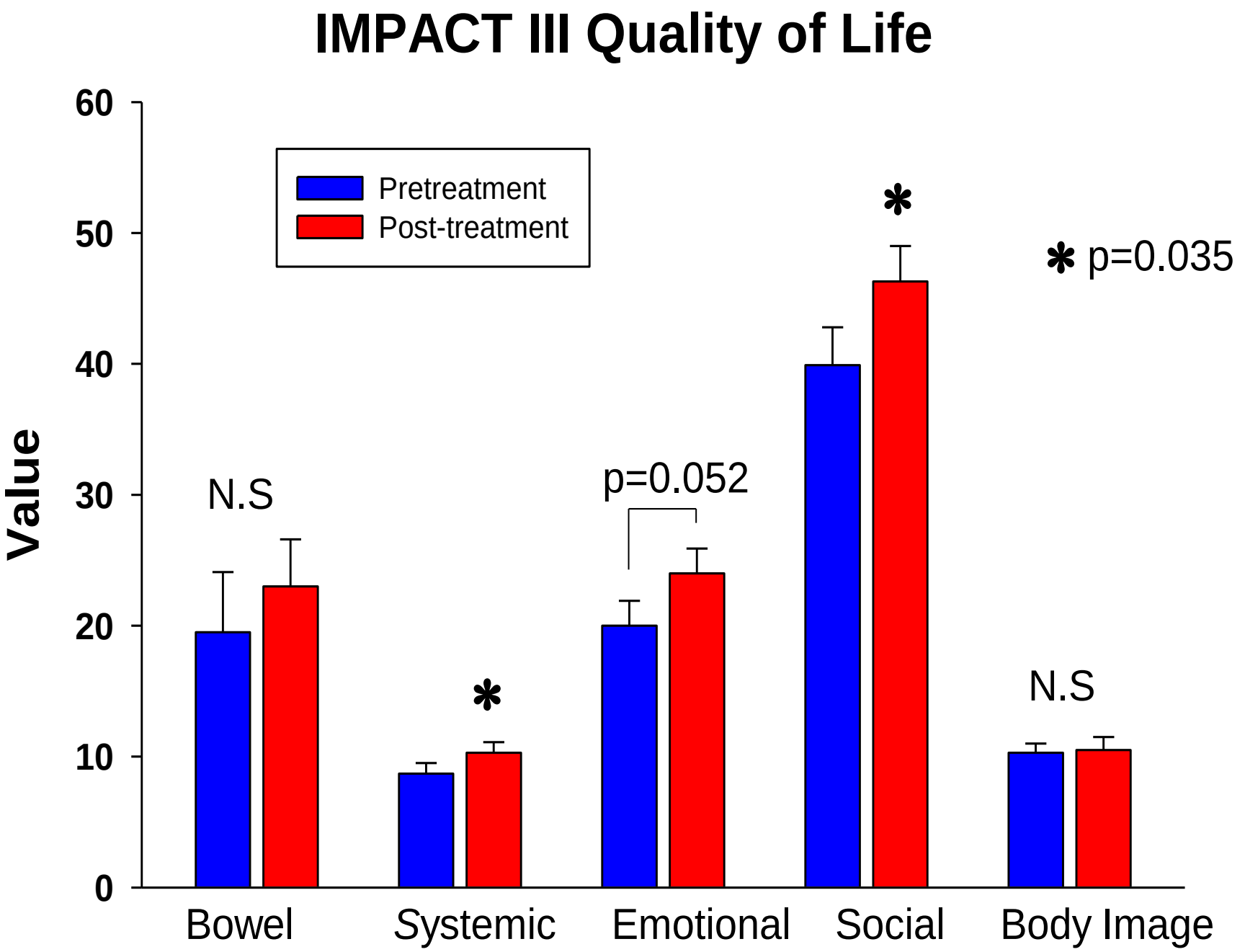
Analysis intent-to-treat

Laboratory Values

Blood Test	Pre-treatment	Post-naltrexone
Prealbumin	15.4 ± 1.4	16.5 ± 1.6 ↑
AST	34.8 ± 2.8	32.9 ± 2.5
ALT	14.5 ± 3.0	11.0 ± 2.4
WBC	8.5 ± 1.3	6.2 ± 0.6 ↓
C-RP	3.5 ± 1.4	2.3 ± 0.8 ↓
ESR	42.3 ± 8.0	38.4 ± 4.0 ↓
Hemoglobin	11.5 ± 0.4	12.0 ± 0.4 ↑

Side Effects

Side Effect /Symptom	Placebo	Naltrexone
Sleep disturbance	2	2
Unusual dreams	0	2
Headache	1	1
twitching	1	0
Decrease appetite	1	0
Nausea	0	1
Hair loss	1	0
Fatigue	1	0
Flushed ears	0	1
Papules rash	1	0
Double vision	0	1


IMPACT III Quality of Life
Value
60
50
40
30
20
10
0
Pretreatment
Post-treatment
* p=0.035
N.S
p=0.052
*
*
N.S
Bowel
Systemic
Emotional
Social
Body Image

Advantages of Naltrexone

- May be administered orally
- Down-regulates but does not eliminate proinflammatory cytokines
- Few side effects
- Once a day dosing
- Cost effective

Think outside the box

- **Why is low dose naltrexone better than higher dose?**
- **Receptor affinity?**
- **What role does NTX have with innate immunity & restoring immune homeostasis?**
- **Is the mechanism of action in autoimmune disorders different than cancer?**
- **Will NTX work better if other immunosuppressive drugs are discontinued?**

Which way to go?

- Secured FDA Orphan drug status in children
- Ulcerative colitis?
- Other autoimmune disorders?

- Patent licensed for development TNI Biotech

TNI Biotech

- TNIB is planning a phase 1 PK trial in healthy volunteers for Dec 2013
- TNIB is planning adult Phase 2b & Phase 3 trials estimated to initiate in 1Q 2014
- Trials will be offered to qualified clinical investigators in the US and EU. Other countries will also be included.
- Adults with moderate to severe Crohn's disease are asked to contact their physician to find out more information
- Patient entry criteria (Inclusion and Exclusion) for the Phase 2b and Phase 3 will be posted in www.clinicaltrial.gov once approved by the appropriate ethics committees and regulatory bodies
- Please visit the TNI BioTech website www.tnibiotech.com for additional information, or to contact the company directly if interested.

Conclusions

1. Naltrexone therapy appears to be effective for active Crohn's disease.
2. Naltrexone therapy is well tolerated, inexpensive, and given orally once a day.
3. The mechanism by which naltrexone works may be through opioid blockade on inflammatory cells, mucosal healing through the OGFr, by augmenting innate immunity, or all of these.
4. There is a need for safe, effective therapy in patients with IBD especially children