

Low Dose Naltrexone Treatment for Crohn's Disease

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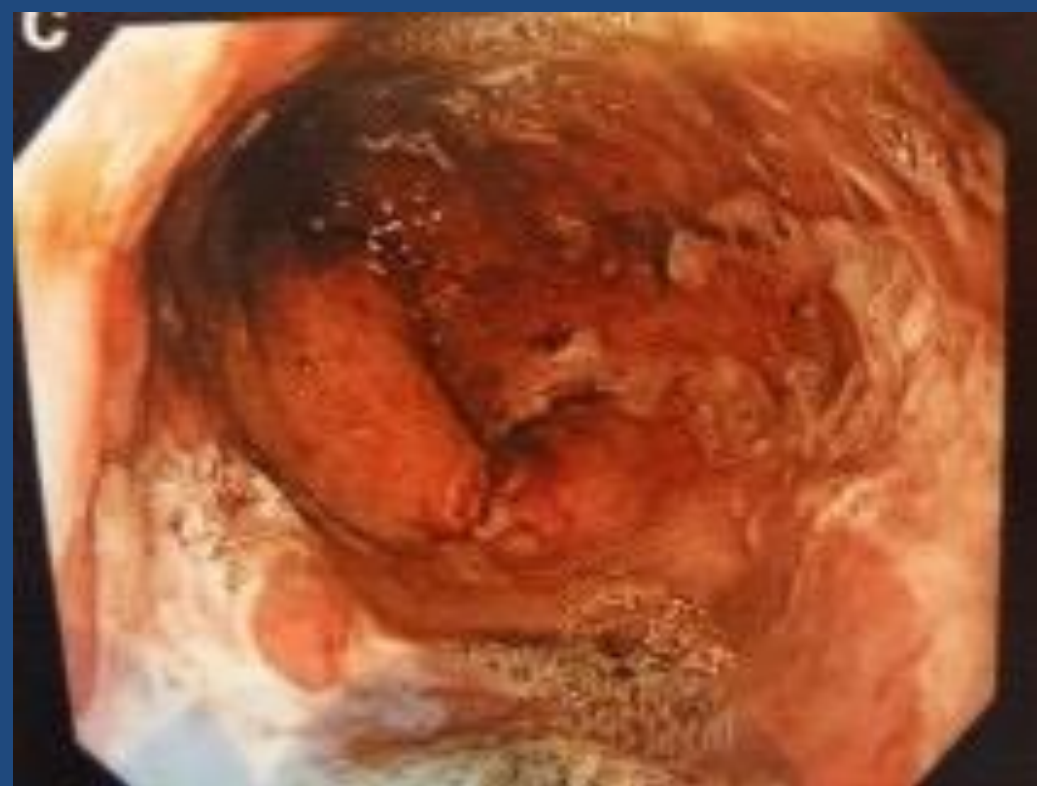
- Member of the Crohn's and Colitis foundation
- Owner of Healing Crohn's and Colitis consulting company
- Physician Assistant 11 specialties since 1982
- Physiologist: University of California, Davis
- National and International lecturer on LDN, Bone Health, Spinal Cord Stimulators
- Medical consultant to Algostim Biotech Company
- Rocky Mountain Pediatric Orthopedics
- No conflict of interests with subject matter

Take Away Points

- Become familiar with Crohn's Disease
- Crohn's Current Therapies
- Arguments for LDN as therapy for Crohn's disease

What is Crohn's Disease

- 1 of 2 major inflammatory bowel diseases not to be confused with irritable bowel
- 1.3 million US citizens, 50,000 children
- Can be severely disabling, Lower incomes
- May involve any place in the GI tract.
- Ulcerative colitis is the other IBD that only involves the colon and more superficial disease. (curable with colectomy)
- Crohn's is transmural can cause fistulas, strictures, abscesses.



Crohn's Symptoms

- Tender abdominal pain
- Fever
- Weight loss
- Childhood stunting of growth
- Diarrhea
- Fatigue

Laboratory findings

- Anemia low Hgb/Hct (blood loss)
- Low protein due to poor absorption
- High C-reactive protein and ESR
Inflammation markers
- Blood in stool
- Upper and lower endoscopy changes

What went wrong to develop Crohn's

- Dysregulation of Innate immune system
- Low endorphins MS, Crohn's, RA according to Dr. Gironi In Milan. Beta endorphins downregulate IL6, IL12
- Increased relative activity of TnF, NfKb, IL6, IL12, reduced IL10
- Patients with IL10 mutation early Crohn's
- Proteins pass by tight junction (one cell layer thick) ignite immune response
- Glocker et al, N. Engl J Med 2009 361: 2033-2045
- Gironi et al, Arch Neurol 2000, Aug 57 (8) 1178-81

More on how does Crohn's develop

- Gluten, casein may form opiate like peptides that bind to the opiate receptors, thus causing more dysregulation on the tissue level and central nervous system.
- Gluteomorphins and casomorphins
- Vitamin D regulates the tight junctions from the Gut to Blood (leaky gut). Many have Vitamin D deficiency

Current traditional therapies

- Corticosteroids: AVN, DM, Cataracts, superinfections, wt gain
- Azathioprine (Imuran),: skin cancer, fatal T cell lymphomas, 3-4x risk but still rare.
- Aspirin based products: GI bleed
- Elemental diet effective but difficult

Biologic Agents Tnf inhibitors

- Blocks Tnf-alpha that reduces inflammatory cytokines
- Infliximab (Remicaide) IgG mouse 75%, human 25% \$3000-\$6000 per infusion
- Adalimumab (Humira) recombinant Human 100% SQ injection
- Significant disease modification
- 38% remission with adalimumab 12% placebo
- Hanauer SB, et al Gastroenterology 2006: 130 (2) 323

Infliximab

- 30.1% mucosal healing
- Side Effects: 25% fatal fungal infections, 3-5x risk of T cell lymphomas (young men mostly), overwhelming infections
- Allergic reactions which make ineffective
- Risks increase with use of other immunomodulators
- Columbelle Jf et al, NEJM 2010

Low Dose Naltrexone Effects

- Increases IL10, Igf-B, transforming growth factor, and NK cells (natural Killer)
- Inhibits Tnf, TH-17, IL6, IL12
- Mice study with Murine IBD reduced IL6, IL12, to normal level reduced wt loss
- Increase endorphins 2-3 fold with AIDS patients . Endorphins modulate T cells
- Bihari B, Enkaphalin in treatment of AIDS-related complex. 1999
- Matters GL et al, Naltrexone improves murine IBD, Journal Immunotoxicology, 2008 Apr; 5(2) 179-187

LDN Studies

- LDN 69% remission 89% responded, Smith JP,
 - Blocks acute endotoxic shock with Tnf inhibition
 - Naltrexone blocks Nk cell buprenorphine suppression
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- Smith JP, et al Low Dose Naltrexone Therapy Improves Active Crohn's Disease, American Journ Gastroenterology, 102 No. 4 (2007); 1-9
 - Greeneltch KM, et al, Brain Behavior Immun, 2004, Sept; 18(5):476-84
 - Boyadjeva et al, Naltrexone disrupts NK cell inhibition, Journal Immuno 2004 , 173:42-49

More LDN Studies

- Jill Smith 40 patients severe Crohn's 4.5 mg naltrexone 12 weeks:
- 89% favorable response,
- 30% remission, increase to 50% after 24 weeks
- 48% Endoscopic improvement LDN, 0% placebo,
- 33% remission 8% placebo
- Complete remission 22% placebo 0%
- Smith JP, etal Safety and tolerability of LDN therapy in Children with moderate-severe Crohn's J. Clin Gastroenterology 2013 Apr; 47(4) 339-45

LDN Promotes Mucosal Healing

- 40 patients with moderate-severe Crohn's disease based on CDAI scores
- 82% has significant CDAI score reduction
- 45% clinical remission (CDAI<150) 78% CDEIS reduction (endoscopic scores)
- 40% placebo lower CDAI scores 28% CDEIS
- Naltrexone no side effects, placebo fatigue
- Smith JP, et al, Therapy with Opioid Antagonist Naltrexone Promotes Mucosal Healing in Active Crohn's disease:a randomized Placebo-Controlled Trial, Dig Dis Sci 2011, 56:2088-2097

LDN ORPHAN DESIGNATION

- In January 2010 Dr. Jill Smith obtains orphan drug designation for the treatment of pediatric Crohn's disease with naltrexone.
- Need to get market approval by a drug company to help change the attitudes of practitioners

My Patient Experiences

- 12 year old girl with Crohn's disease for several years August 2015
- Cramping losing weight fatigued inflammatory markers CRP and ESR elevated, Stool Calprotectin elevated
- October 2015 on LDN 2 months, gained 12 pounds, CRP, ESR normalized, Calprotectin lowered, no cramps no symptoms
- GI DOC "What happened this is like a miracle"

Ulcerative Colitis patient

- 23 yo male with UC for several years with bloody diarrheal stools cramping
- After 6 weeks on LDN “I had my first normal stools in over a year for 5 days.”

Drugs are not the only answer to Crohn's

- Vitamin D3: inhibits NOD gene, increases AMP, reduces Tnf, tight junction proteins
- Omega 3FA inhibit inflammation
- Probiotics: immunoregulation of the gut microbiome 300 species 100 trillion in gut
- Dietary changes: gluten, casein
- Glutamine to feed the enterocytes and cell synthesis

Summary

- Crohn's has significant disability and suffering that can affect anywhere in the GI tract
- Many therapies: steroids, 6MP, azathioprine, ASA, biologics but have inherent risks and can be costly.
- LDN may be just as effective
- \$40/mo,
- no serious side effects.
- May be considered primary treatment or after initial failure on other treatments