Low Dose Naltrexone
Exciting clinical applications

Disclosures

Sahar Swidan

- o Speaker's Bureau: (Amgen)
- o Employment: (Pharmacy Solutions)

TD1

This continuing education activity is managed and accredited by AffinityCE/Professional Education Services Group (ACE/PESG) in cooperation with A4M. ACE/PESG as well as all accrediting organization do not support or endorse any product or service mentioned in this activity.

ACE/PESG and A4M staff as well as Planners and Reviewers has no relevant financial or nonfinancial interest to disclose.

Commercial Support was not received for this activity.

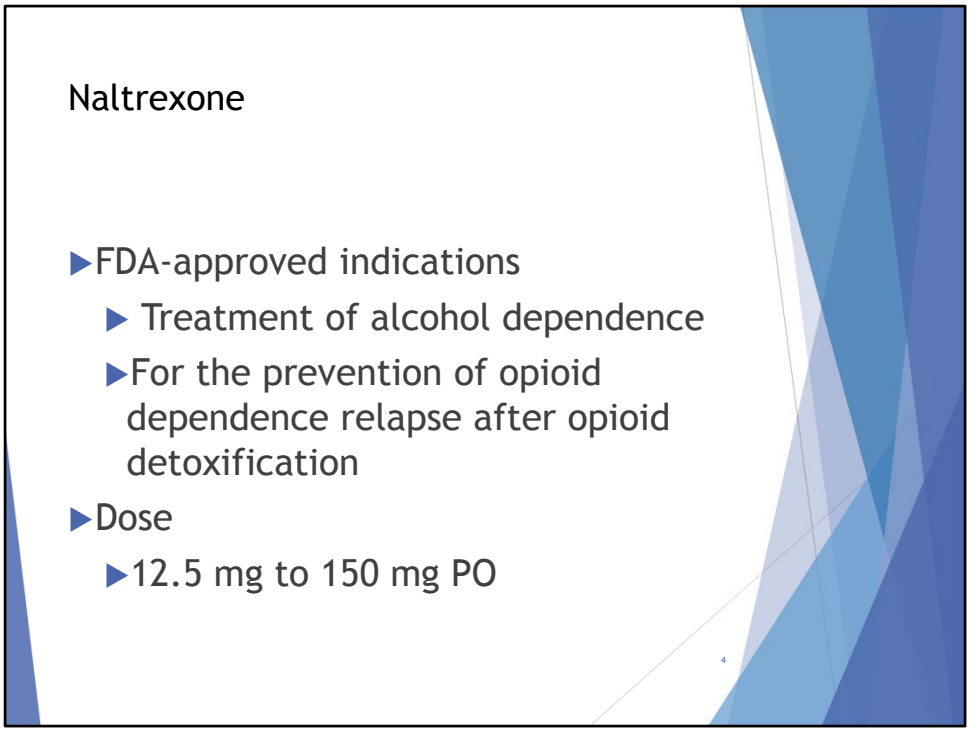
Slide 2

TD1 this should match the disclosure you submitted. If you have changes since you submitted your disclosure, we ask that you resubmit.
Tiffany Duke, 8/8/2018

Objectives

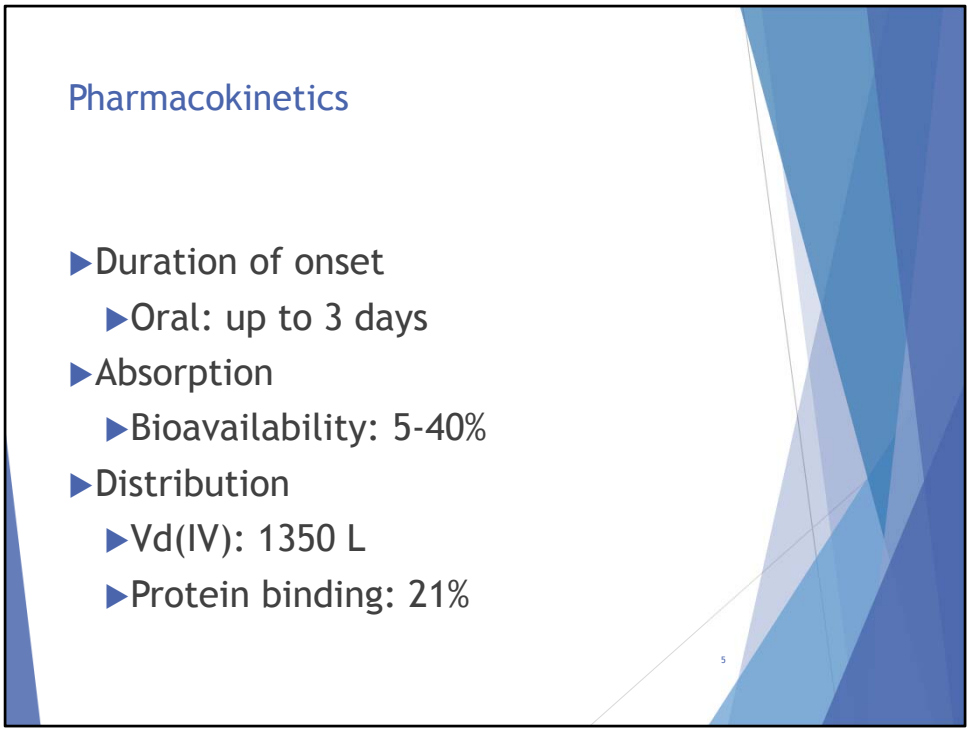
- Review traditional uses of naltrexone
  - Mechanism of action
  - Pharmacokinetics
- Discuss the immune modulating respond of low dose naltrexone
- Discuss off-label uses for naltrexone
  - Crohn's Disease
  - Autism
  - Multiple Sclerosis
  - Chronic Pain
  - Cancer
  - Many others

3

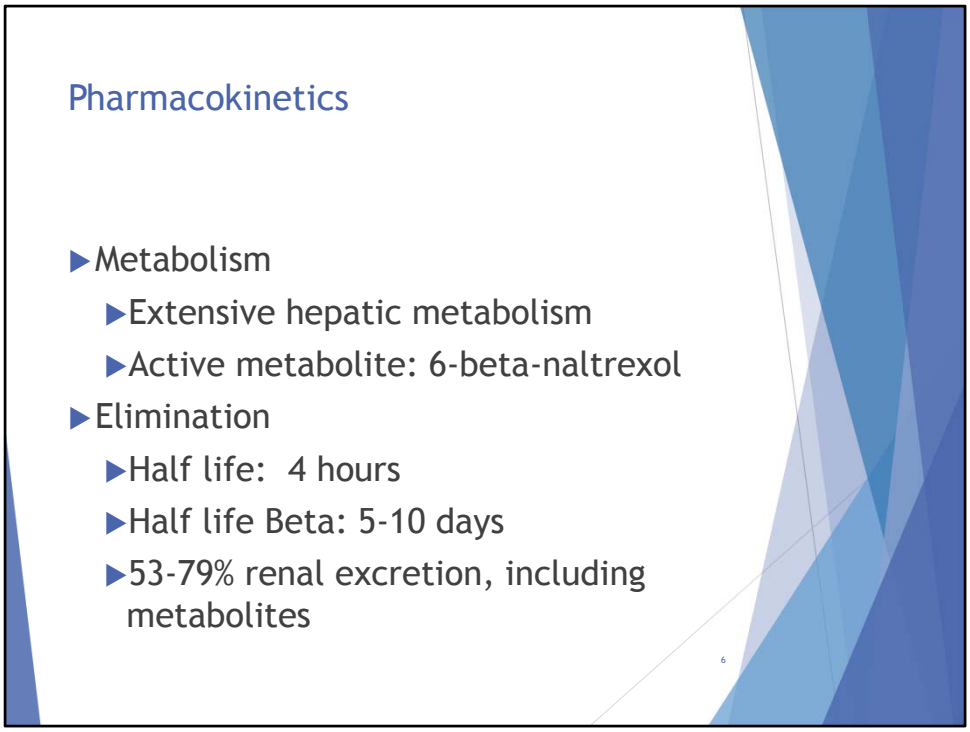


Naltrexone micromedec, fc

Must be opioid free before administration
Dose- depends


Pharmacokinetics
Duration of onset
Oral: up to 3 days
Absorption
Bioavailability: 5-40%
Distribution
Vd(IV): 1350 L
Protein binding: 21%
5

Keep?



Keep?

Micromedex states elimination half life is 5-10 days (dependent on erosion of the polymer)

Contraindications

- Acute hepatitis
- Liver failure
- Recent or current opioid/alcohol ingestion

WHAT IS LOW DOSE NALTREXONE (LDN)

- Naltrexone belongs to a class of drugs known as opioid antagonists
- Naltrexone blocks opiate drugs from binding to the opioid receptors, which can result in increased **endorphin** and **enkephalin** release.
  - Endorphins and enkephalins are the body's natural painkillers.
  - These natural peptide chemicals produced in your body interact with receptors in your brain to help you feel focused, less impacted by pain and put you in a better mood.

History of Naltrexone …

NALTREXONE - 50mg-200mg

- 1963 – Synthesized
- 1967 – Patented
- 1984 – FDA Approval for Heroin Addiction = 50mg dose
- 1991 – Yale studies, Alcoholism. 2x successful as placebo
- 1995 – FDA approval for alcoholism
- 2003 – Vitriol
- 2005 – Yale studies Obesity | Contrave
- FDA approval orphan drug Autism

History of LDN…

LOW-DOSE NALTREXONE 0.5mg - 4.5mg

- 1985 – Dr. Bihari – Harvard MD, treatment of AIDS patient
  - AIDS patients 20% normal endorphin levels
  - KEY DISCOVERY – 1% normal dose paradoxical effect
    300% increase in endorphin levels
  - Best success rate in the country
- 2007 1st LDN Research Article – Crohn's Disease, Penn State
- 2009 Fibromyalgia – Stanford Medical School
- PUBMED = 230 LDN Articles

Many Diseases are Expressions of a Malfunctioning Immune System

- Immune system is regulated by endorphins
- Endorphins have a primary action on opiate receptors
- Briefly blocking opiate receptors up-regulates endorphins
- Acts in an immunomodulatory way to correct the immune system
- Cell growth (proliferation) can be mediated by endorphins
- Cell proliferation may be suppressed by endorphins

HOW DOES LDN Help Your Immune System, Reduce Pain, Inflammation and Autoimmune Conditions ?

- Down regulates inflammatory cytokine release, oncogene expression and auto-immune cascades
- In the Central Nervous System **(CNS)**
  - Reduces toll-like receptor (TLR) signaling and glial cell activation resulting in reduced inflammatory cytokines and reduced neuro-inflammation
- In the Peripheral Nervous System **(PNS)**
  - Modulates T & B lymphocyte production (example: gut inflammation)
  - Reduces inflammatory cytokines (IL6, IL12, TNF alpha)
  - Suppresses tumor growth factor (NF-kB)

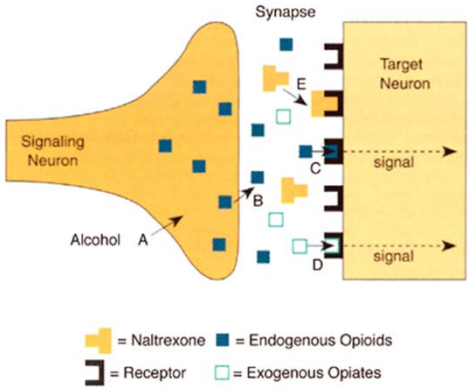
When taken at bedtime, the short acting LDN binds to the receptors which leads to a brief blockade of opioid receptors between 2 am and 4 am. This blockade is believed to up-regulate vital elements of the immune system by causing an increase in endorphin and enkephalin production

Naltrexone and Toll Like Receptors (TLRs)

- Naltrexone is an antagonist of TLRs
- TLR Activation leads to production of **NF-ķB** (inflammatory signaling pathway)
  - NF-ķB linked to expression of cancer oncogenes
    - Cancer oncogenes turn off natural cell death mechanism
    - Leads to uncontrolled growth of cancer cells

Mechanism of Action

- Antagonist of opiate receptors
- Highest affinity: mu opioid receptor



14

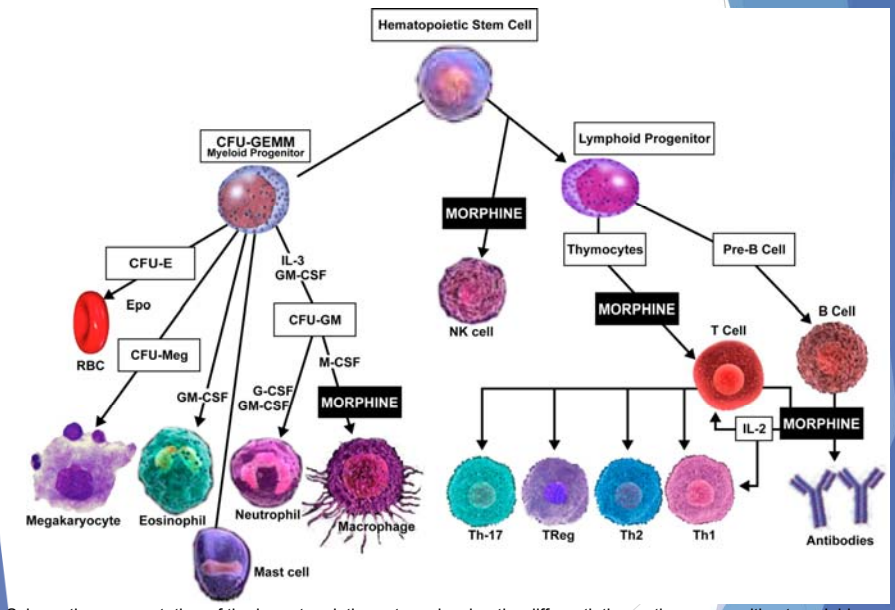
Naltrexone and Toll Like Receptors (TLRs)

- Naltrexone is an antagonist of TLRs
- TLRs lead to production of pro-inflammatory cytokines when activated
- Pro-inflammatory cytokines increase inflammation
- Pro-inflammatory cytokines increase pain

Low Dose Naltrexone

17

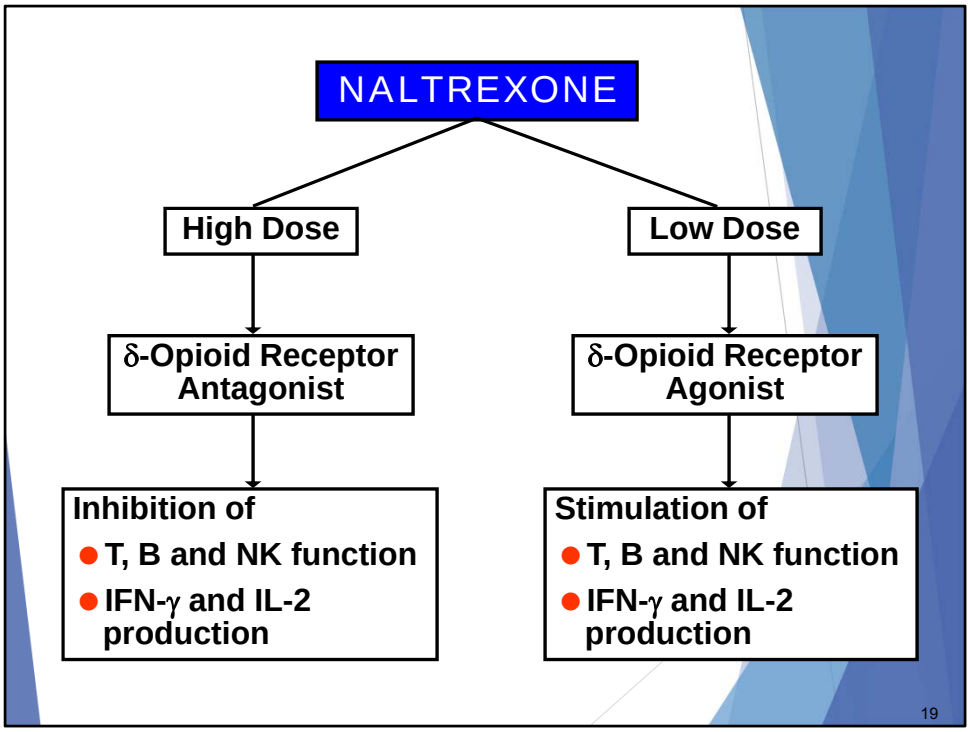
Effects of Opioids on the Immune System

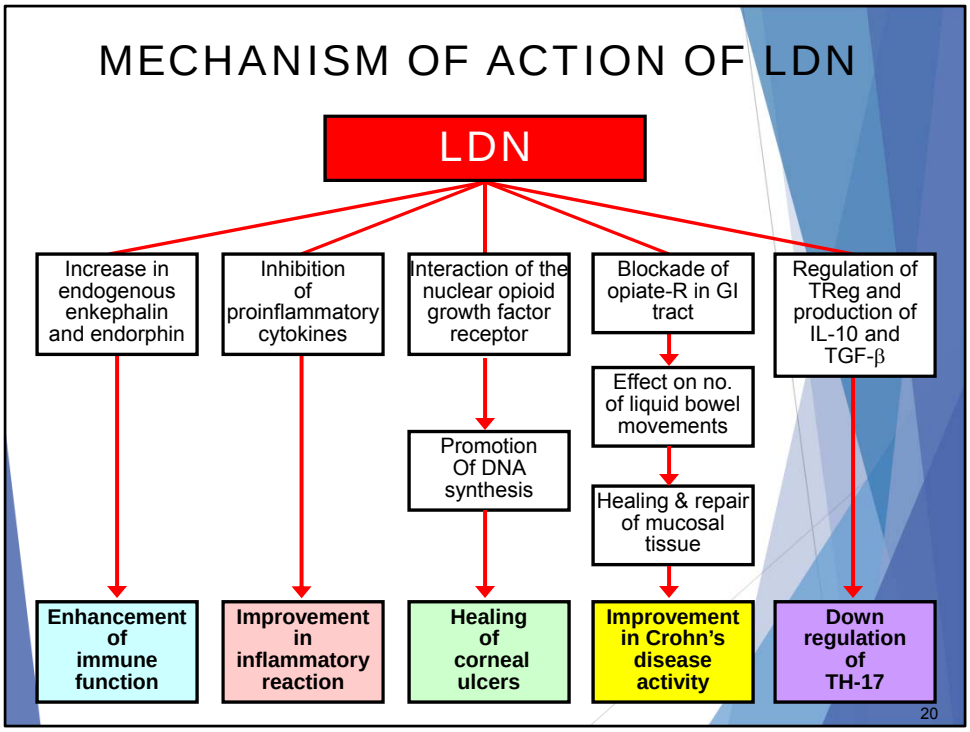


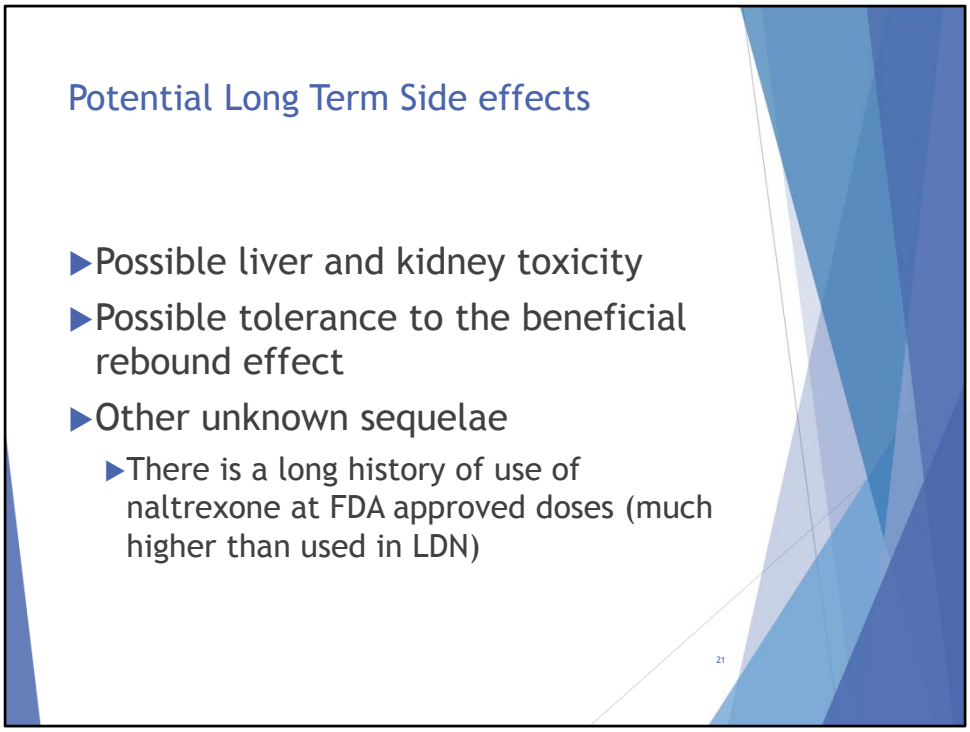
Schematic representation of the hematopoietic system showing the differentiation pathways sensitive to opioids.

from Effects of Opioids on the Immune System – Roy S. and Loh H.H., Neurochemical Research, 21:1375-1386, 1996

18

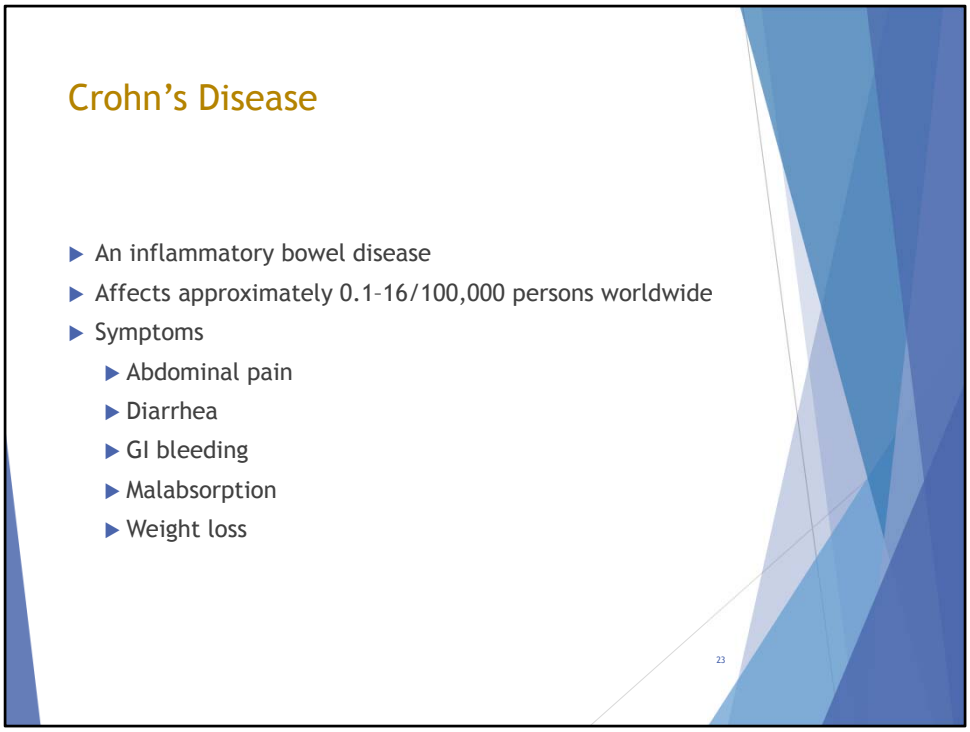

NALTREXONE
High Dose
Low Dose
δ-Opioid Receptor Antagonist
δ-Opioid Receptor Agonist
Inhibition of
T, B and NK function
IFN-γ and IL-2 production
Stimulation of
T, B and NK function
IFN-γ and IL-2 production
19


MECHANISM OF ACTION OF LDN
LDN
Increase in endogenous enkephalin and endorphin
Inhibition of proinflammatory cytokines
Interaction of the nuclear opioid growth factor receptor
Blockade of opiate-R in GI tract
Regulation of TReg and production of IL-10 and TGF-β
Promotion Of DNA synthesis
Effect on no. of liquid bowel movements
Healing & repair of mucosal tissue
Enhancement of immune function
Improvement in inflammatory reaction
Healing of corneal ulcers
Improvement in Crohn's disease activity
Down regulation of TH-17
20

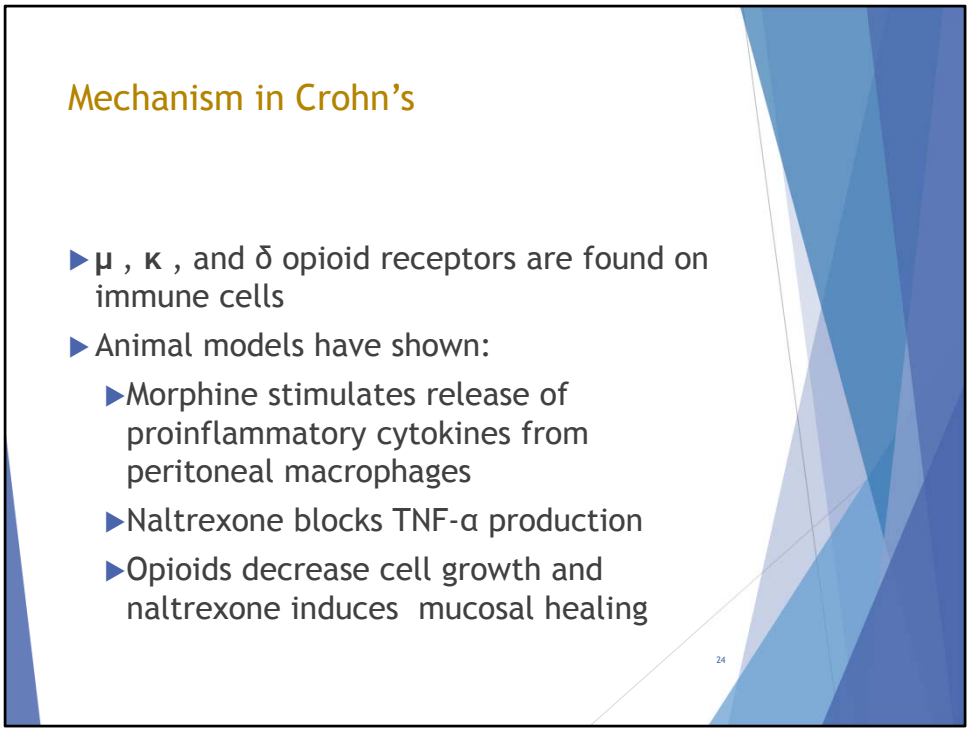


http://www.ldnscience.org/questions-and-answers/low-dose-naltrexone-ldn

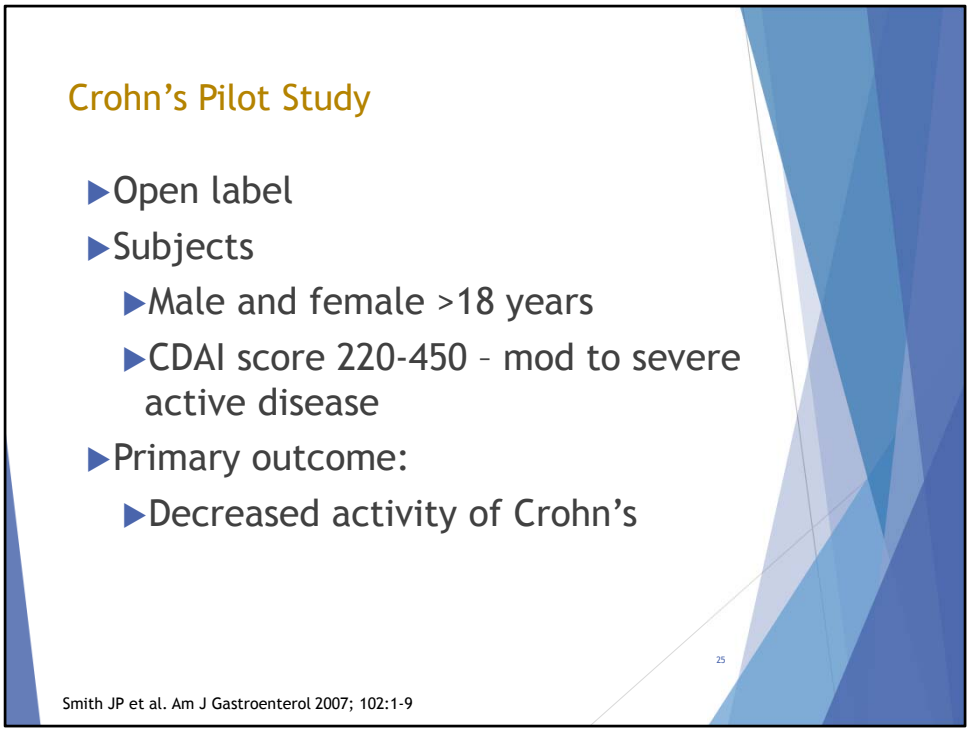

Crohn’s Disease
22



http://www.cdc.gov/ibd/



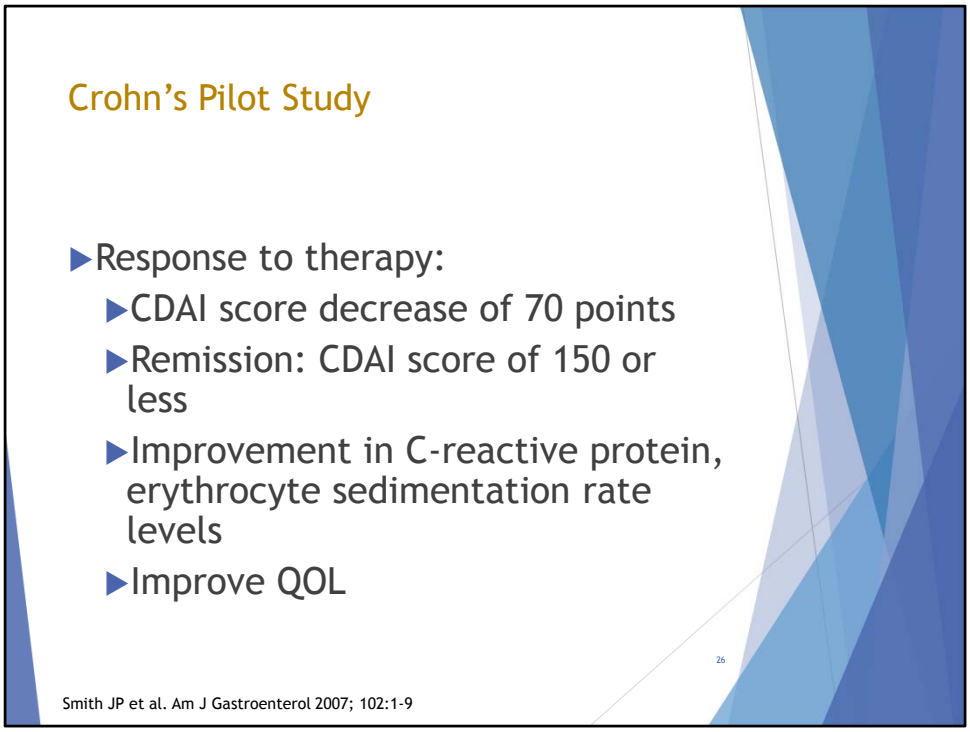
TNF-alpha is an inflammatory mediator



Inclusion
[-cDAI score involves:
Clinical or laboratory variable **Weighting factor**
Number of liquid or soft stools each day for seven days x 2
Abdominal pain (graded from 0-3 on severity) each day for seven days x 5
General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days x 7
Presence of complications* x 20
Taking Lomitil or opiates for diarrhea x 30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite) x 10

Hematocrit of <0.47 in men and <0.42 in women x 6
Percentage deviation from standard weight x 1]

- Patients taking stable doses of aminosalicylates, immunomodulators, corticosteroids, or antibioticswere permitted to enter the study, andwere continued at the same dosage
Exclusion
an ileostomy, colostomy, ileorectal anastomosis, or short bowel syndrome from surgery, and patients with abnormal LFTs. Subjects taking tacrolimus, cyclosporine, mycophenolate, or
infliximab within 8 wk of enrollment were excluded



Inclusion
[-cDAI score involves:
Clinical or laboratory variable **Weighting factor**
Number of liquid or soft stools each day for seven days x 2
Abdominal pain (graded from 0-3 on severity) each day for seven days x 5
General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days x 7
Presence of complications* x 20
Taking Lomitil or opiates for diarrhea x 30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite) x 10

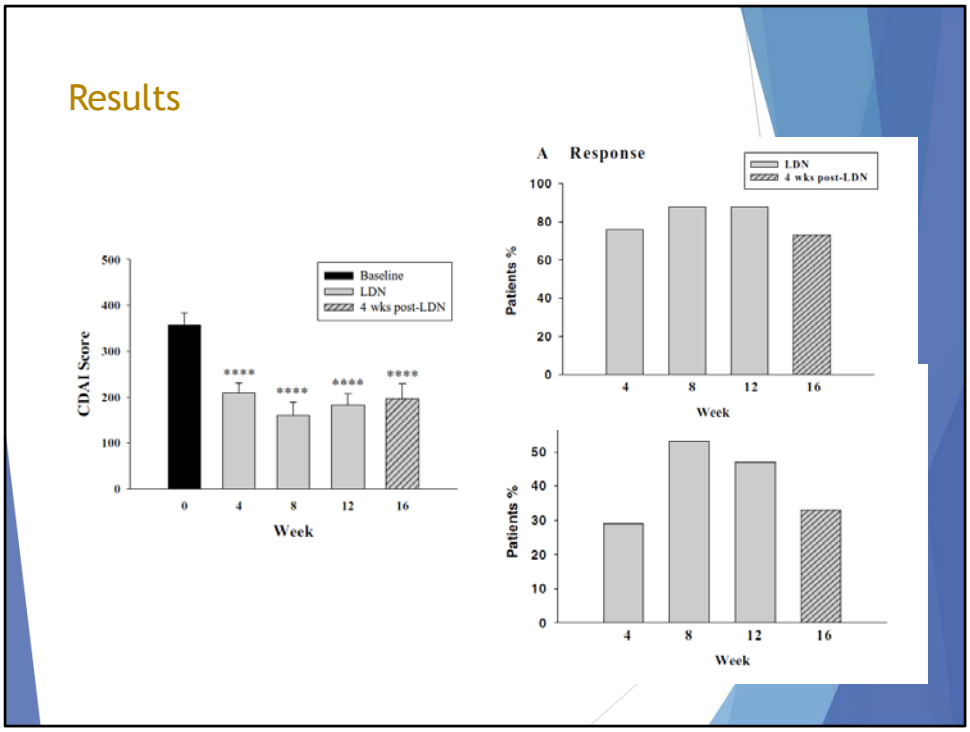
Hematocrit of <0.47 in men and <0.42 in women x 6
Percentage deviation from standard weight x 1]

- Patients taking stable doses of aminosalicylates, immunomodulators, corticosteroids, or antibioticswere permitted to enter the study, andwere continued at the same dosage
Exclusion
an ileostomy, colostomy, ileorectal anastomosis, or short bowel syndrome from surgery, and patients with abnormal LFTs. Subjects taking tacrolimus, cyclosporine, mycophenolate, or
infliximab within 8 wk of enrollment were excluded

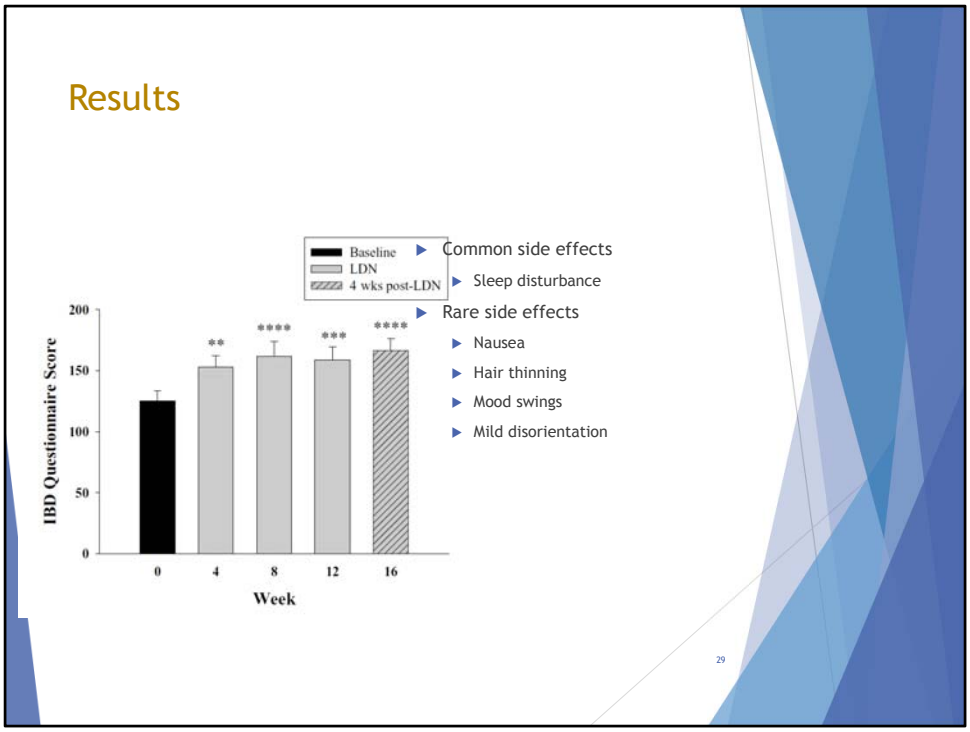
Baseline

- N = 17 subjects
- Naltrexone 4.5 mg at bedtime x 3 months
- Assessed CDAI score
  - Over 7 days before starting study drug
  - Every 4 weeks during trial
  - At week 4 post study drug
- Patients were allowed to continue on aminosalicylates, immunomodulators, corticosteroids, or antibiotics if stable

27



F1: Mean Crohn's disease activity index (CDAI) scores +/- SEM are shown at baseline (wk 0), wk 4, 8, and 12 after initiation of LDN therapy and 4 wk after discontinuation of LDN therapy (wk
16). ****Signi**fi**cantly different from baseline at P < 0.0001
F2: percent of patients responding with a decline in CDAI score of at least 70 points (**A**), % of patients remission by a CDAI score of 150 or less
(**B**), to LDN therapy are shown at wk 4, 8, and 12 and 4 wk after discontinuation of LDN herapy (wk 16).



F3: Mean inflammatory bowel disease questionnaire (IBDQ)
Significantly different from baseline at $**P < 0.01$, $***P < 0.001$, and $****P < 0.0001$.

Discussion

- Fast onset of symptom benefit, 4 weeks
  - Immunomodulators take up to 3-4months
    - Relapse immediately after stopping therapy
- LDN showed continued benefit at 4 weeks post therapy
- Patients had improved QOL

30

Smith et al. 2011

- Prospective, double-blind, randomized, placebo controlled
- Primary outcome
  - Proportion of patients decrease 70 points on their CDAI score
- Secondary outcome
  - Mucosal healing confirmed via colonoscopy and biopsy
- Followed by 12 wk open label extended trial
  - To compare safety and efficacy

31

Smith JP et al. Dis Dis Sci 2011; 56;2088-97

Baseline

- N = 40
- Patients with confirmed moderate to severe Crohn's (CDAI score ≥ 220)
- Randomized to naltrexone 4.5 mg or placebo x 12 wks
- Colonoscopy performed at baseline and 12 wks

32

Baseline

- CDAI score evaluated every 4 wks
- Concomitant medications allowed at same dose throughout study
  - Aminosalicylates, steroids, thiopurines
  - Anti-TNF-α and Lomotil not allowed

33

Results

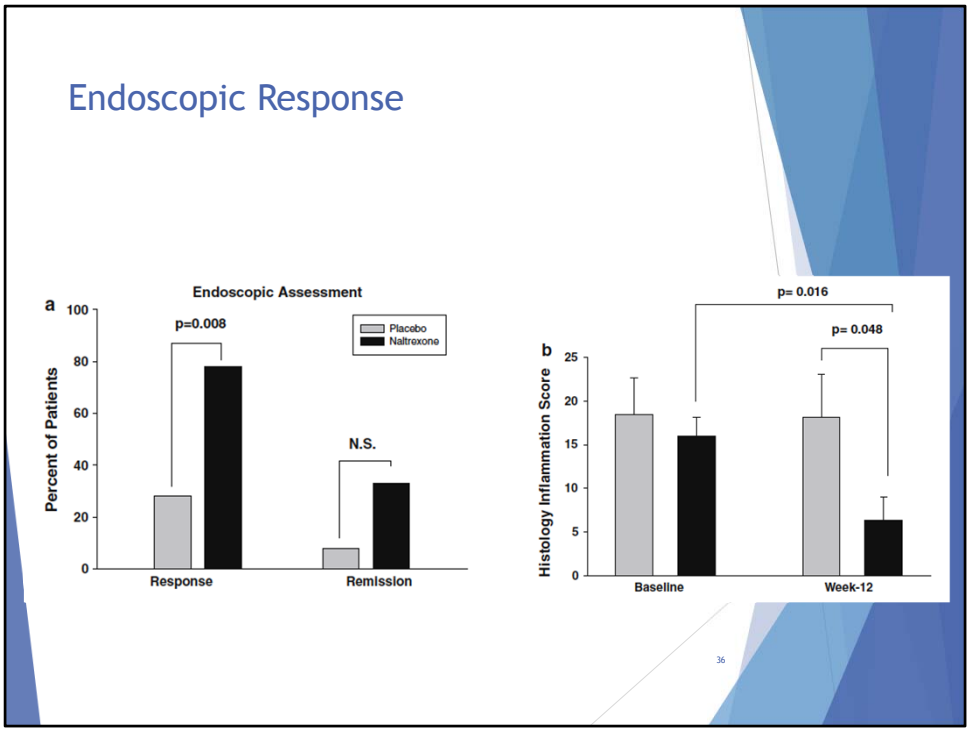
- Primary outcome: at 12 weeks, proportion of patients achieving 70 point decline
  - Naltrexone 88%
  - Placebo 40%
  - p = 0.009

34

Results

- Secondary outcome: mucosal improvement
  - Naltrexone: endoscopic scores improved 48% compared to baseline
    - Endoscopic scores improved 36% compared to placebo
  - Placebo: no improvement in scores

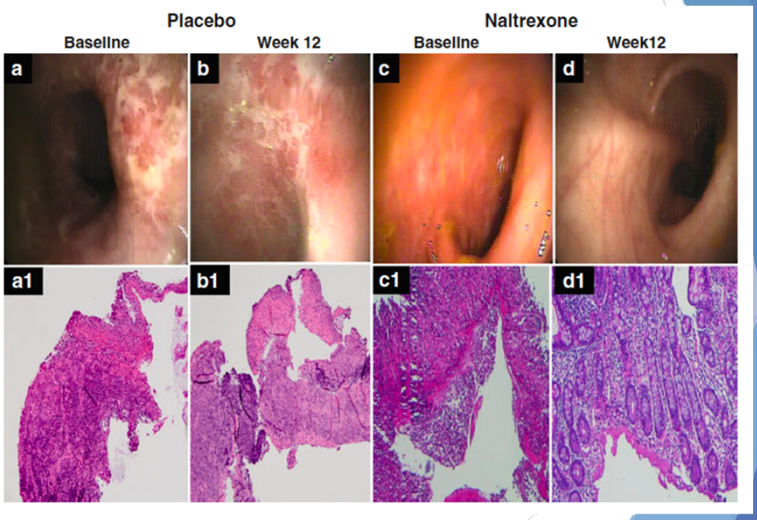
35



A: NtX 78% had endoscopic response (indicated by 5 point dec CDEIS score), 33% had remission (CDEIS <6)
Pb 28% response, 8% in remission
CDEIS = crohn's disease endoscopy index severity

B: histology
NTX vs. PB: p = 0.048 – significant improvement
NTX compared to baseline: p = 0.016
Pb compared to baseline: p = 0.06

Example of Endoscopy



A-D: representative of endoscopy
A→ B no change in erythema, edema, ulceration, loss of vascularity
C→ D mucosal healing
A1-D1: representative histologic chances
A1 → c1 crypt distortion, no improvement
B1→ D1 crypt restoration

Open-Label Extension

- Patients initially treated with naltrexone:
  - Had further CDAI score decrease of 75 points
  - 50% achieved remission
  - No further histologic improvement
- Patients initially treated with placebo
  - Decrease in endoscopic scores by 65%
  - Decrease in inflammation by 36%

38

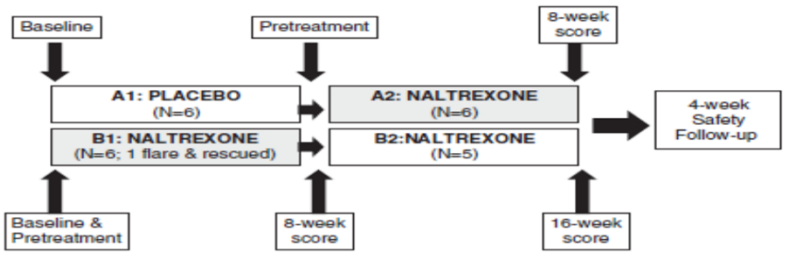
Discussion

- Quality of life greatly improved in naltrexone patients compared to placebo
- Side effects
  - Mostly the same between naltrexone and placebo
    - Except more fatigue in placebo group
- 1 patient in each group dropped out due to flare of disease

39

Phase 1 pilot trial

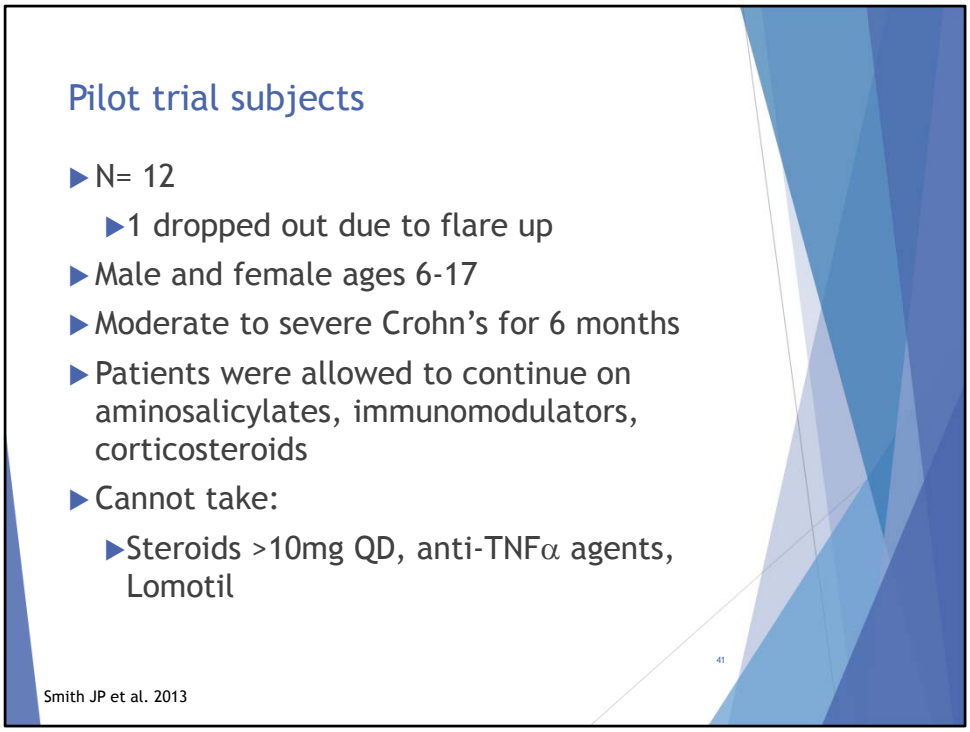
- Psuedo-cross over design
- Primary Outcome
  - Safety and tolerability compared to placebo



40

Smith JP et al. 2013

PCDAI- Pediatric Crohn's Disease Activity Index Scores

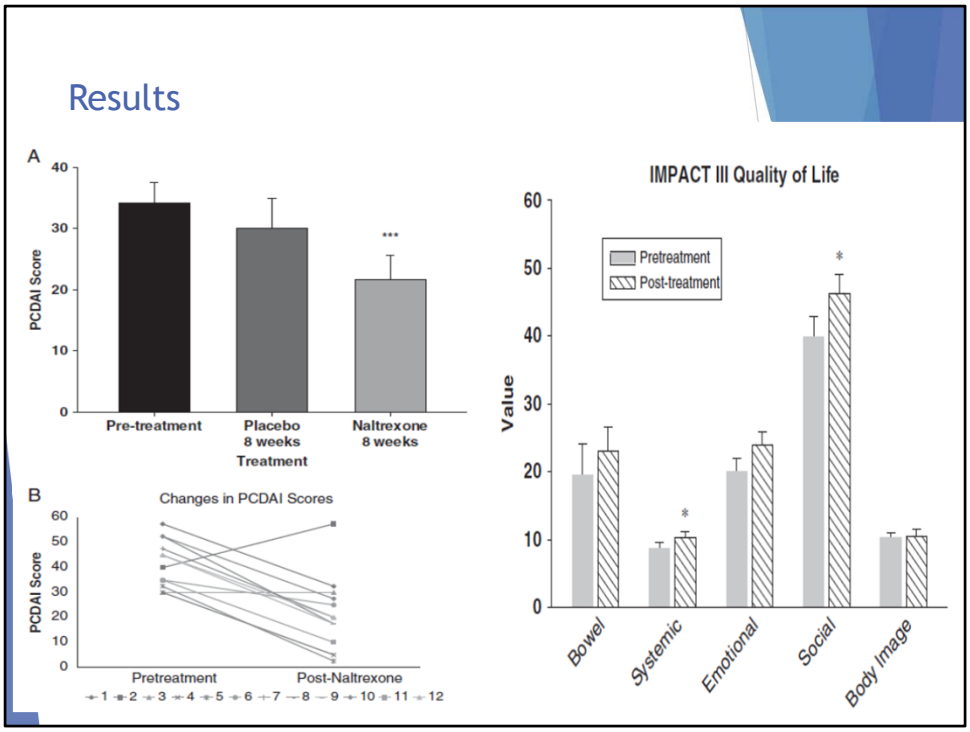


PCDAI >30 for moderate to severe
Must be diagnosed by endoscopic or radiographic methods and had the disease for at least 6 months
Must be taking maintenance medications Aminosalicylates and steroids for at least 4 weeks, immunomodulators for 12 weeks
No biologics, 8 week wash out period before baseline measurements
No abnormal liver enzymes LFTs

Intervention

- Children 10 and older and above 45kg
  - 4.5mg naltrexone/placebo in #4 capsule
- Children <10 years old or under 45kg
  - 0.1mg/kg naltrexone liquid formulation
- Adverse Effects
  - Minimal
  - No difference between placebo and treatment
- No significant changes in lab values including serum transaminases

Smith JP et al. 2013



Significant improvement was observed (P=0.005) when comparing pretreatment PCDAI scores (34.2±3.3) to scores after 8 weeks on naltrexone therapy (21.7±3.9) (Fig. 2A). Only naltrexonetreated subjects and not placebo-treated subjects had PCDAI scores <30 after the first 8 weeks.
Figure 2B comparing baseline values to those at the end of the study (P=0.001). One subject experienced a flare in Crohn's symptoms during the study. Twenty-five percent of those treated with naltrexone were considered in remission (scorer10) and 67% had improved with mild disease activity (decrease PCDAI score by at least 10 points) at the end of the study.
Results of the IMPACT III quality of Life Survey are shown in Figure 3. Two categories significantly improved during the course of this study from baseline (P=0.035) with administration of naltrexone including the systemic symptoms and social well-being.

25% achieved a clinical
remission and 67% had a significant response to therapy, which is higher than what would be expected for a spontaneous response.

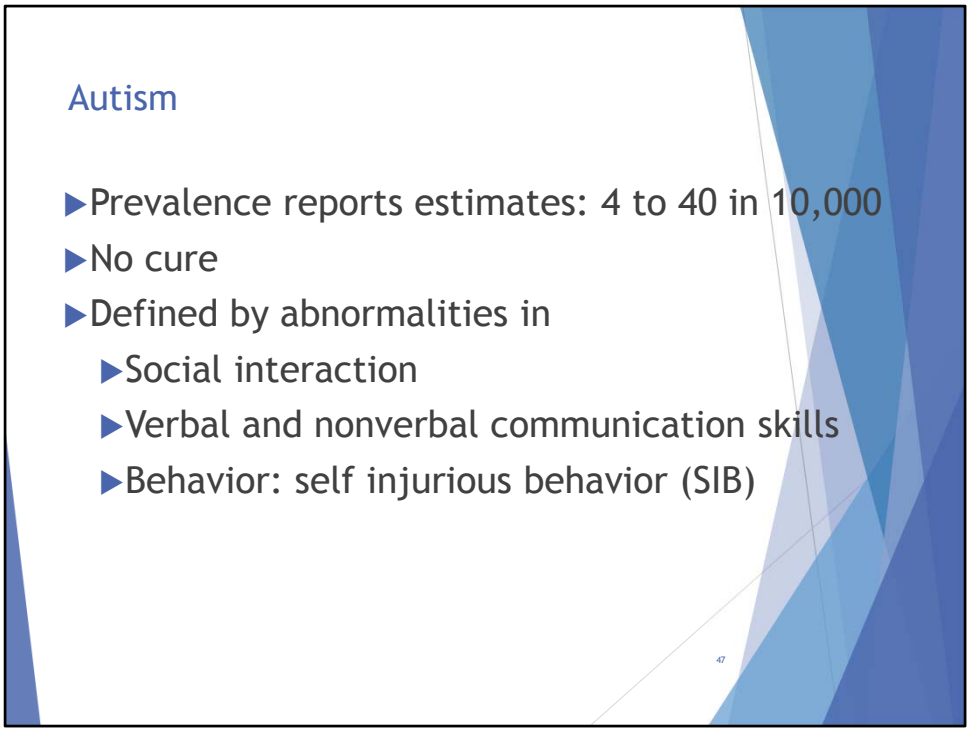
This article is saved in my folder in the shared drive.

Summary of Crohn's

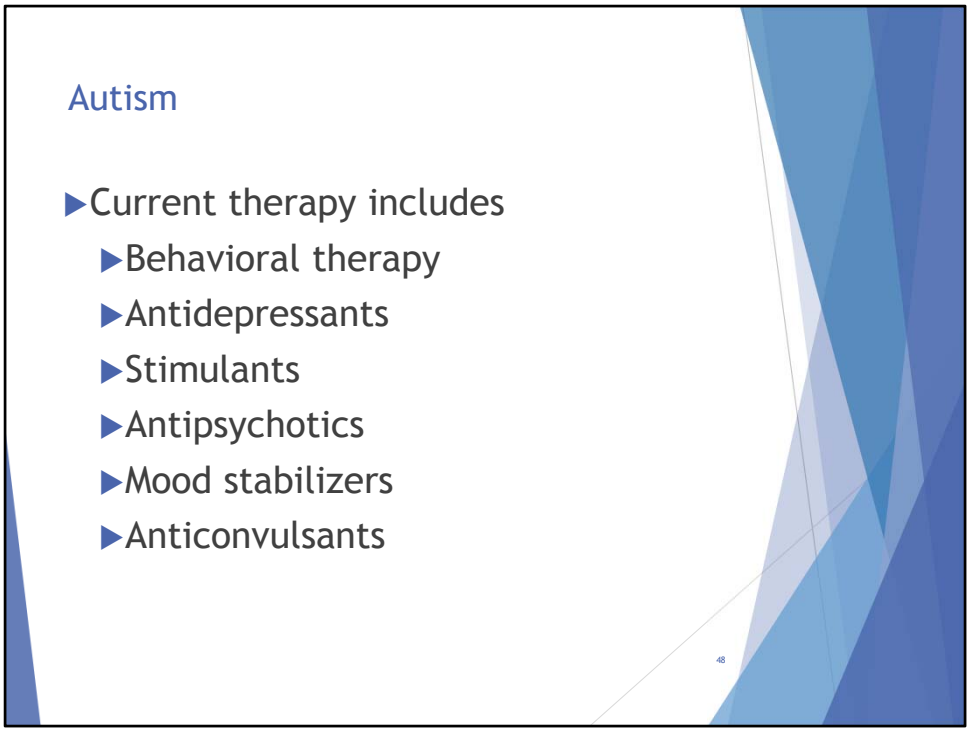
- LDN shows benefit at the mucosal level
- Patients have increased quality of life
- LDN has low to infrequent side effects
- Does not cause immune suppression
- Low cost
- Easy compliance for patients: 1 capsule a day
- Future directions: longer follow-up, synergism with current Crohn's therapy

45

AUTISM



Current therapy has side effects and lack of consistent benefit



Current therapy has side effects and lack of consistent benefit

Autism and Opioids

- In animal models given opioids, behavior abnormalities exhibited were similar to autistic children
  - High tolerance for pain
  - Decreased social interaction
  - Preoccupation with repetitive behavior
- ß- endorphins flooding the brain prevent brain development and maturity

journal of Neuroimmunology

Journal of Neuroimmunology (In Press)

Journal of Neuroimmunology

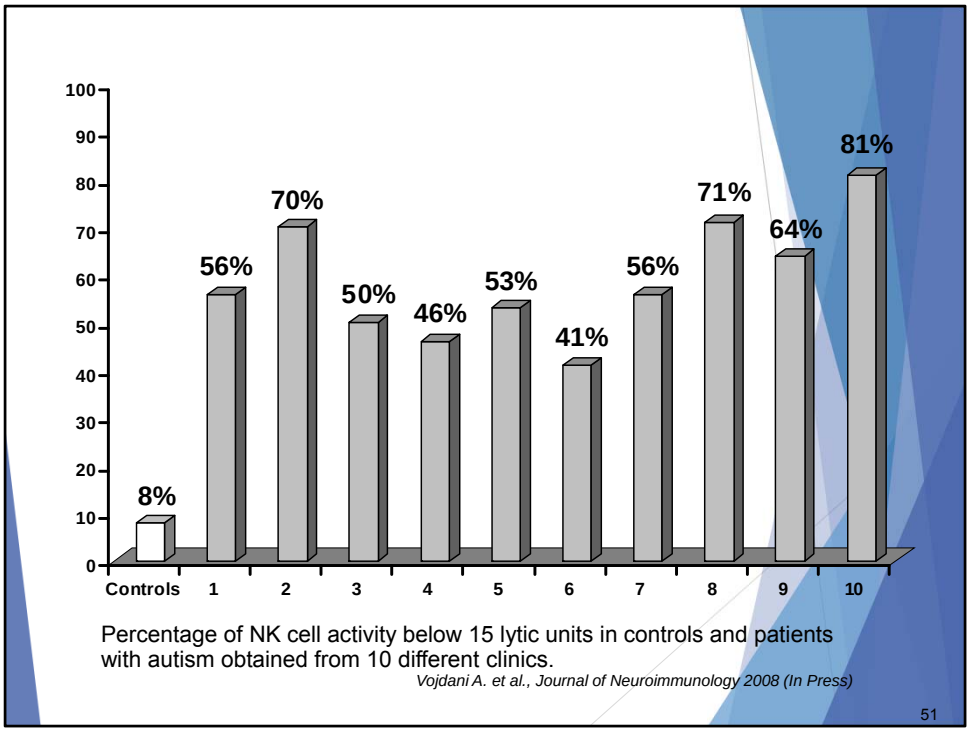
www.elsevier.com/locate/jneuroim

Low natural killer cell cytotoxic activity in autism: the role of glutathione, IL-2 and IL-15

A. Vojdani, et al.

Although many articles have reported immune abnormalities in autism, NK cell activity has only been examined in one study of 31 patients, of whom 12 were found to have reduced NK activity. The mechanism behind this low NK cell activity was not explored. For this reason, we explored the measurement of NK cell activity in 1027 blood samples from autistic children obtained from ten clinics and compared the results to 113 healthy controls. This counting of NK cells and the measurement of their lytic activity enabled us to express the NK cell activity/100 cells. At the cutoff of 15-50 LU we found that NK cell activity was low in 41-81% of the patients from the different clinics. This NK cell activity below 15 LU was found in only 8% of healthy subjects ($p < 0.001$). Low NK cell activity was not correlated with age. The induction of NK cell activity by IL-2, IL-15 and glutathione was more pronounced in a subgroup with very low NK cell activity. We conclude that 45% of a subgroup of children with autism suffers from low NK cell activity, and that low intracellular levels of glutathione, IL-2 and IL-15 may be responsible.

"The induction of NK cell activity by IL-2, IL-15 and glutathione was more pronounced in a subgroup with very low NK cell activity. We conclude that 45% of a subgroup of children with autism suffers from low NK cell activity, and that low intracellular levels of glutathione, IL-2 and IL-15 may be responsible."



Percentage of NK cell activity below 15 lytic units in controls and patients with autism obtained from 10 different clinics.

Vojdani A. et al., Journal of Neuroimmunology 2008 (In Press)

51

Antibodies to Neuron-Specific Antigens in Children with Autism: Possible Cross-Reaction with Encephalitogenic Proteins from Milk, *Chlamydia pneumoniae* and *Streptococcus* Group A
***Journal of Neuroimmunology*, 129:168-177 2002**
A. Vojdani, A.W. Campbell, E. Anyanwu, A. Kashanian, K. Bock, E. Vojdani

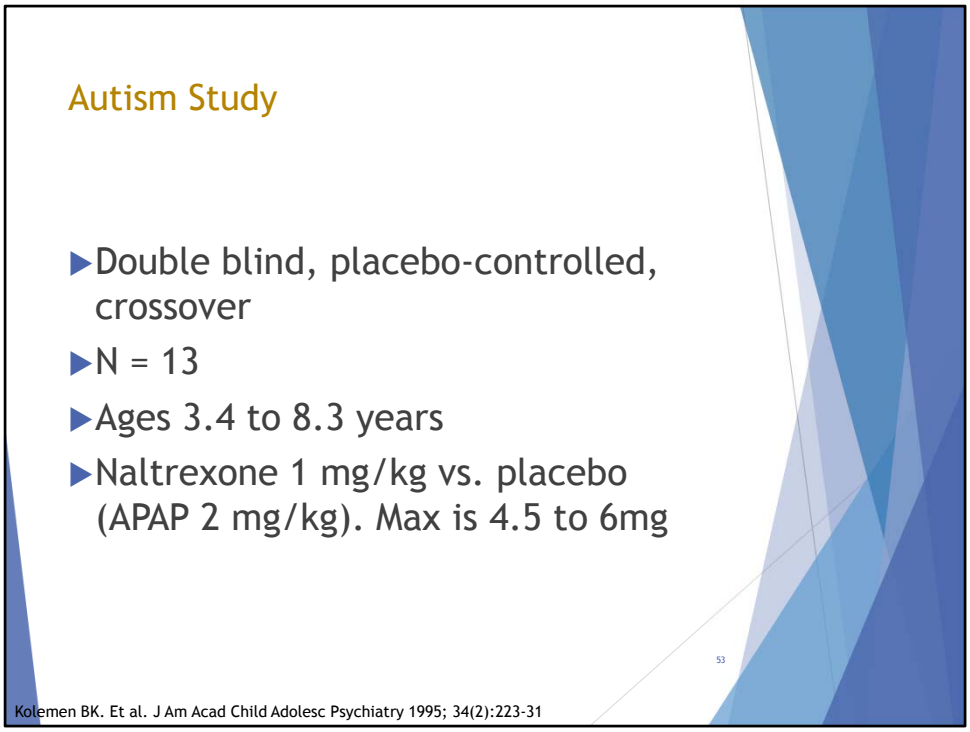
Infections, Toxic Chemicals and Dietary Peptides Binding to Lymphocyte Receptors and Tissue Enzymes are Major Instigators of Autoimmunity in Autism
***Int J Immunopathol Pharmacol* 16(3):189-199, 2003**
A. Vojdani, J.B. Pangborn, E. Vojdani, E.L.Cooper

Heat Shock Protein and Gliadin Peptide Promote Development of Peptidase Antibodies in Children with Autism and Patients with Autoimmune Disease
***Clin Diag Lab Immunol* 11(3):515-524, 2004**
A. Vojdani, M. Bazargan, E. Vojdani, J. Samadi, A.A. Nourian, N. Eghbalieh, E.L. Cooper

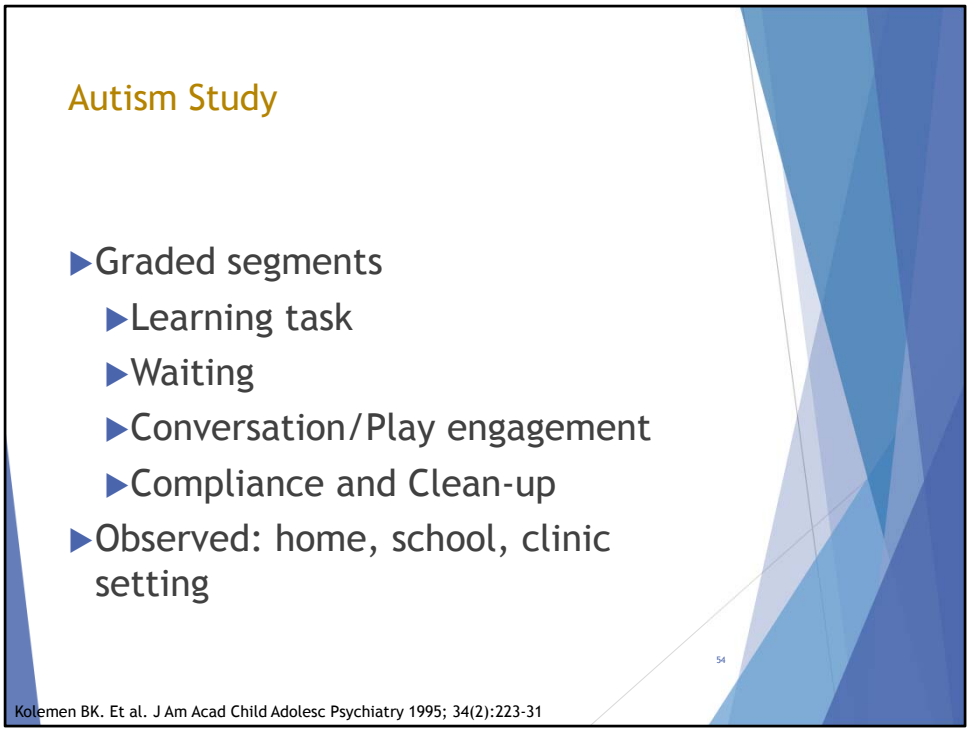
Immune Response to Dietary Proteins, Gliadin and Cerebellar Peptides in Children with Autism
***Nutritional Neuroscience*, 7(3):151-161, 2004**
Vojdani, T. O'Bryan, J.A. Green, J. McCandless, K.N. Woeller, E. Vojdani, A.A. Nourian, E.L. Cooper

Antibodies against Central Nervous System Antigens in Autism: Possible Cross-Reaction with Dietary Proteins and Infectious Agent Antigens.
***Neuropsychiatric Disorders & Infections*, pp 171-186, 2005, S.H. Fatemi (ed), Taylor & Francis Ltd**
Vojdani, T. O'Bryan, J.A. Green, J. McCandless, K.N. Woeller, E. Vojdani, A.A. Nourian, E.L. Cooper

52



APAP to match bitter taste



APAP to match bitter taste

Design

Group	Practice and Baseline	First Phase	Washout	Second Phase
1: Placebo First	7 days/ 7 days	14 days	2 days	12 days
2: Drug First	7 days/ 7 days	14 days	7 days	14 days

- Longer washout for group 2 due to half life of naltrexone binding in the brain
- Measures
  - CGI rating of global improvement
  - Conners Parent Rating Scale, included impulsivity/hyperactivity factor
  - Conners Teacher Rating Scale, included impulsivity/hyperactivity factor
  - Naltrexone Side-Effects Scale
  - Children's Psychiatric Rating Scale (CPRS)

55

t/2 72-108h

Results- Home and School Setting

TABLE 3

Summary Values for Parent and Teacher Ratings during Baseline, Placebo, and Naltrexone Trials with *p* Values for Significance of Difference: Naltrexone versus Baseline and Naltrexone versus Placebo

Measure	Baseline Mean	Baseline SD	Placebo Mean	Placebo SD	Naltrexone Mean	Naltrexone SD	*p* Value[a] vs. Baseline	*p* Value[a] vs. Placebo
Parent CGI[c] (n = 11)	4.0	0.0	4.3	1.2	3.0	1.1	.0001[b]	.007
Parent IHF[d] (n = 12)	1.8	0.8	1.9	1.0	1.3	0.8	.012	.011
Parent SE-Restlessness[e] (n = 11)	2.3	1.3	2.5	1.2	1.7	0.8	.0107[b]	.006
Teacher CGI[c] (n = 13)	4.0	0.0	4.1	1.0	3.4	0.9	.0164[b]	.016
Teacher HF[f] (n = 13)	1.9	0.9	1.9	0.6	1.7	0.8	.049	.272
Teacher SE-Restlessness[e] (n = 13)	3.8	1.5	3.4	1.4	2.5	1.3	.060	.067

[a] *p* Value using two-tailed paired *t* tests for comparison between placebo and naltrexone trials unless otherwise indicated.
[b] *p* Value using Wilcoxon (nonparametric) test.
[c] CGI = Clinical Global Impressions Improvement: 1 = very much improved to 4 = no change to 7 = very much worse.
[d] Parent IHF = Conners Parent Rating Scale Impulsivity-Hyperactivity Factor.
[e] Restlessness item on Naltrexone Side-Effects Rating Scale: 1 = no symptoms to 5 = severe and constant symptoms.
[f] Teacher HF = Conners Teacher Rating Scale Hyperactivity Factor.

56

Parents and teachers saw significant difference in behavior on most scales, can see that parents thought they saw much better improvement than teachers

Results – Clinic Setting

TABLE 4
Summary Values for Clinical Measures during Baseline, Placebo, and Naltrexone Trials

Measure	Baseline		Placebo		Naltrexone	
	Mean	SD	Mean	SD	Mean	SD
CGI[a] (n = 13)	4	0	3.8	1.0	3.3	1.1*
Actometer[b] (n = 7)	94	3	97	87	78	49**
On-task[c] (n = 13)	29	35	33	36	33.2	24.1
Communication initiations[d] (n = 13)	8.3	9.3	14	21	23	31*
Disruptive behavior[d] (n = 13)	21	30	17	26	19	28
Self-stimulation[d] (n = 13)	10	17	29	30	26	28*
CPRS[e] stereopathies (n = 12)	2.8	0.9	2.7	3.0	2.7	2.8

[a] CGI = Clinical Global Impressions Improvement: 1 = very much improved to 4 = no change to 7 = very much worse, baseline = no change.
[b] Actometer = total measurement for waiting, conversation, compliance, and pick-up segments.
[c] Percent of 10-second intervals on-task for entire interval.
[d] Percent of 10-second intervals in which behavior occurred.
[e] CPRS = Children's Psychiatric Rating Scale.
* $p \leq .10$ unadjusted for developmental quotient (DQ); p = not significant (NS) adjusted for DQ, using a one-way analysis of variance with repeated-measure design. ** $p < .05$ adjusted for DQ; NS unadjusted, using a one-way analysis of variance with repeated-measure design.

57

Results from clinic setting, saw NO significant differences
Actometer- monitors movement, was attached to child's right leg

Discussion

- Children were considered improved if they improved in 2 out of 3 settings
  - 8/13 were improved
  - 3 of the 8 improved in all three settings
- Most common side effects
  - Drowsiness
  - 2 children had increase in aggressive behavior

58

SMALL SAMPLE SIZE

Summary of Autism Studies

- Doses used: 0.5 – 2 mg/kg
- Age: 3-19 years
- Diagnosis: autism with or without SIB
- N ranged from 5 – 41 patients

59

ElChaar GM et al. Ann Pharmacother 2006; 40:1086-95

Summary of Autism Studies

- Positive outcomes found
  - Decreased hyperactivity
  - Decreased hostility and SIB
  - Improved communication and sociability

ElChaar GM et al. Ann Pharmacother 2006; 40:1086-95

Autism Summary

- Many small trials show some encouraging results but not all were able to show significance
  - Scales used have some subjective component which may lead to biased results

61

Autism Summary

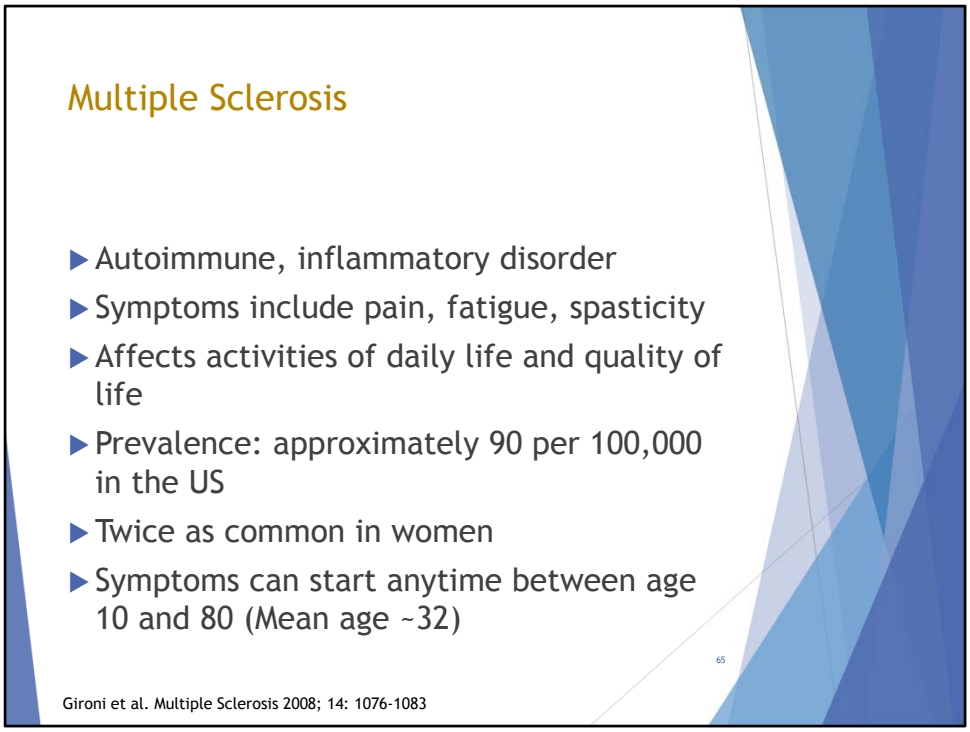
- Most common side effects: sedation, bitter taste
- Other side effects
  - Reduced appetite
  - Vomiting
- Generally used when most other therapies have failed

62

ROUTE of Naltrexone?

- Oral route maybe better if the patient complains of constipation and cramps
- Bitter taste- MUST COMPOUND APPROPRIATELY to mask flavor
- Transdermal route should be used if child complains of diarrhea
- Naltrexone 6mg/mL in Anhydrous PLO gel
- Apply at HS

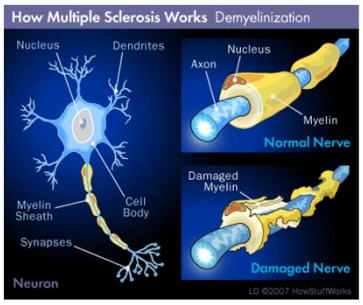
Multiple Sclerosis

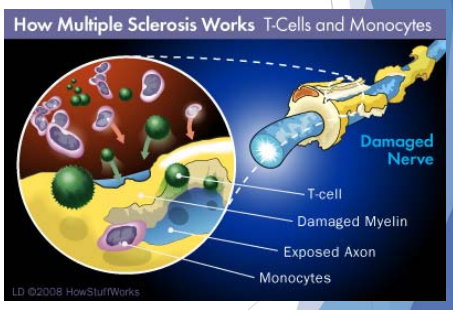


http://health.howstuffworks.com/diseases-conditions/musculoskeletal/multiple-sclerosis2.htm
http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/neurology/multiple_sclerosis/

Pathophysiology

- Caused by demyelination of neurons





Mechanism of Naltrexone

- Short term blockade causes increase in endogenous opioid release
- ß- endorphins are involved in nociception, mood, endocrine secretion and food intake
  - Recently found to have anti-nociceptive and anti-inflammatory activity

Gironi et al. Multiple Sclerosis 2008; 14: 1076-1083

Medical Hypotheses (2005) 64, 721–724

medical hypotheses

ELSEVIER

medical hypotheses

http://intl.elsevierhealth.com/journals/mehy

Low-dose naltrexone therapy in multiple sclerosis

Agrawal Y.P.

The use of low doses of naltrexone for the treatment of multiple sclerosis (MS) enjoys a worldwide following amongst MS patients. There is overwhelming anecdotal evidence, that in low doses naltrexone not only prevents relapses in MS but also reduces the progression of the disease. **It is proposed that naltrexone acts by reducing apoptosis of oligodendrocytes. It does this by reducing inducible nitric oxide synthase activity.** This results in a decrease in the formation of peroxynitrites, which in turn prevent the inhibition of the glutamate transporters. Thus, the excitatory neurotoxicity of glutamate on neuronal cells and oligodendrocytes via activation of the a-amino-3- hydroxy-5-methyl-isoxazole-4-propionic acid class of glutamate receptor is prevented. It is crucial that the medical community respond to patient needs and investigate this drug in a clinical trial.

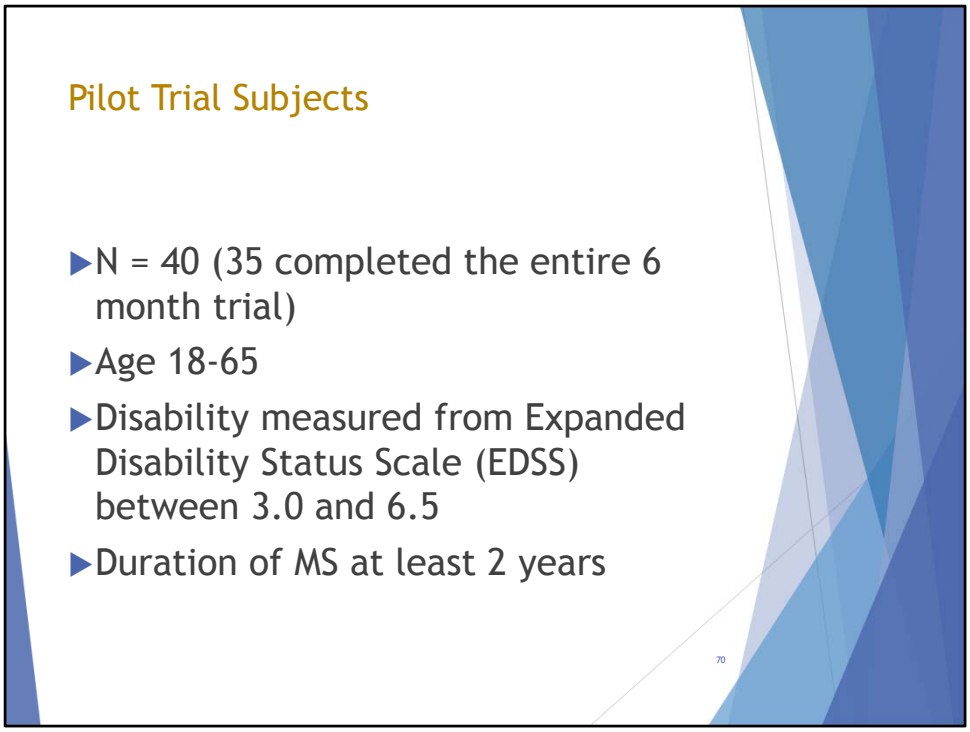
68

LDN and Multiple Sclerosis

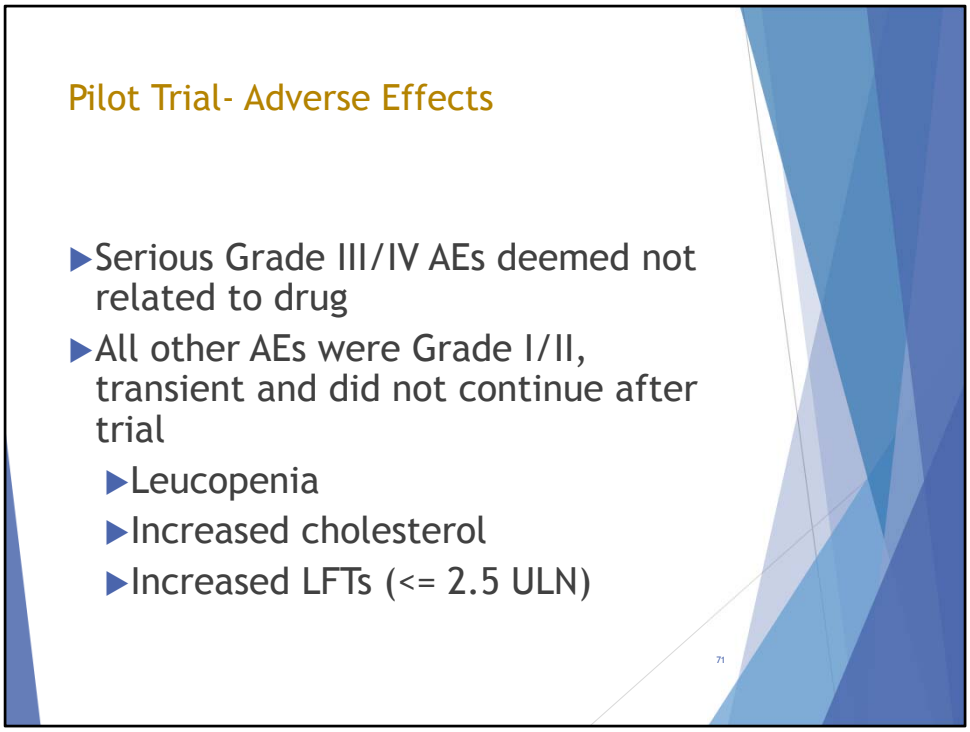
- Open label, uncontrolled, multi-center in Italy
- Treatment for 6 months
- Primary outcome: safety and tolerability
- Secondary outcomes
  - Efficacy for fatigue, pain, spasticity, depression
  - Quality of life
- Started at 2 mg at bedtime x 4 weeks, then increased to 4 mg

69

Gironi et al. Multiple Sclerosis 2008; 14: 1076-1083



At the time of inclusion, patients should be 18–65 years aged, had a disability level measured with the Expanded Disability Status Scale (EDSS) [15] between 3.0 and 6.5, had to have a disease duration longer than 2 years, and had a stable disease course in the 6 months before the enrollment. Patients were enrolled if they were affected by at least one of the following symptoms: spasticity (defined as a score between 2 and 4 in, at least, one limb on the Modified Ashworth Scale) [16], pain [defined as a score >2 at the Visual Analogue Scale (VAS)] [17], fatigue [measured with a score between 36 and 63 at the Fatigue Severity Scale (FSS)] [18], and/or depression [measured with a score >9 at the Beck Depression Inventory] [19].

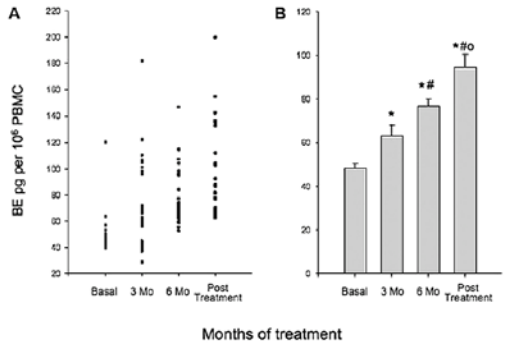


5 withdrew because of: 1. enuresis (bedwetting), 1.worsening hyposthenia (abormal weakness of limbs), 1. >2fold incr bili, 1. UTI causing renal failure (h/o of polycystic kidney disease, serious), 1. pt using tramadol for pain, 1. bony metastases from lung carcinoma (serious)

Results

Table 4 Effect of low-dose naltrexone administration in primary progressive multiple sclerosis patients on spasticity, fatigue, pain, and depression during the 6 months study

Secondary outcome measures	No. of patients[a]	Baseline value (median)	Final value (median)	% improved	% stable	% worsened	*P* value
Spasticity (Modified Ashworth Scale)	38	0.87	0.5	47.4%	42.1%	10.5%	0.008
Fatigue (Fatigue Severity Scale)	39	45	44	33.3%	25.6%	41%	0.51
Pain (Visual Analogue Scale)	39	2	3	28.2%	15.4%	56.4%	0.01
Depression (Beck Depression Inventory scale)	36	5	4.5	55.6%	11.1%	33.3%	0.09



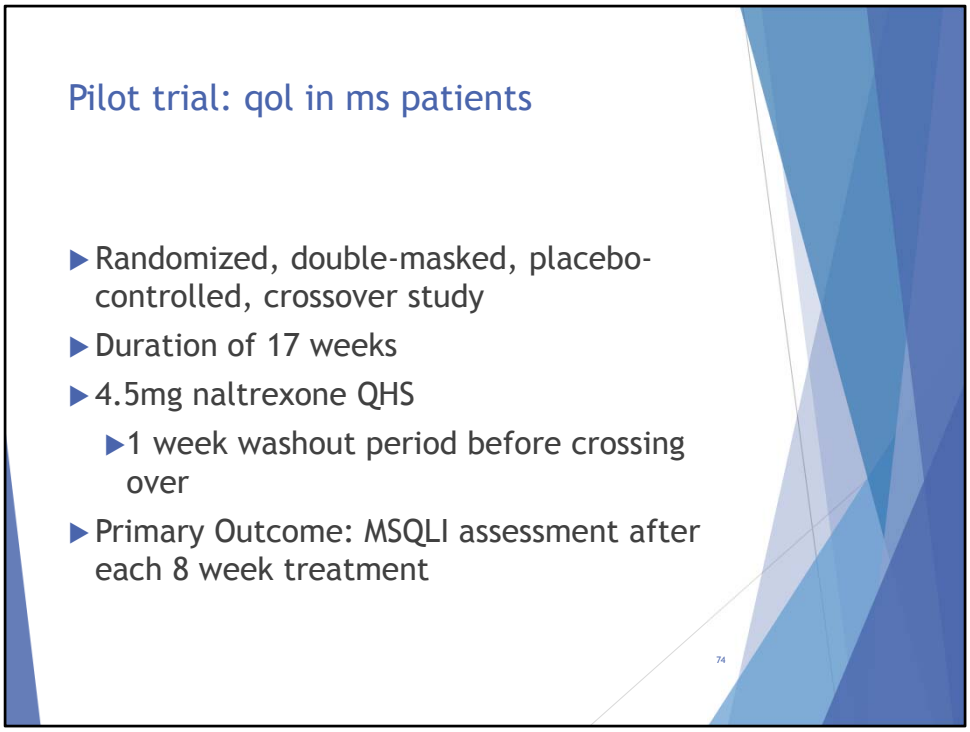
Results: showed LDN only significant in spascity symptom
Also trend towards improvement in symptoms as Be levels increased over trial time

Expanded Disability Status Scale (EDSS)
BE – beta endorphin
PBMC – peripheral blood mononuclear cells
MOR – mu opioid receptor

Summary

- After 6 months of LDN, only significant benefit was in spasticity
  - Corresponded to increase in B-endorphin
  - Remained elevated after discontinuation for 1 month
- Low side effect profile
- Patients felt improvement in QOL but results were not significant

73



The MSQLI6 is a QOL assessment tool developed for MS composed of 11 rating scales: the Physical Component Summary (PCS) and Mental Component Summary (MCS) of the Short Form-36 General Health Survey (SF-36),7,8 Mental Health Inventory (MHI), Pain Effects Scale (PES), Perceived Deficits Questionnaire (PDQ), Multiple Sclerosis Social Support Survey (MSSS), Modified Fatigue Impact Scale (MFIS), Impact of Visual Impairment Scale (IVIS), Bowel Control Scale (BWCS), Bladder Control Scale (BLCS), and the Sexual Satisfaction Scale (SSS)

*****Improvement in QOL is characterized by an increase in the scores for the PCS, MCS, MHI, and MSSS and a decrease in scores for the MFIS, PES, PDQ, BWCS, BLCS, IVIS, and SSS.

Subjects

- N= 80
  - 10 dropped out
  - 10 dropped from analysis due to errors and/or uncompleted surveys
- Ages 18-75
- Must not change or initiate disease-modifying or symptomatic therapies during trial
- Exclusions
  - Starting a disease-modifying drug in the last 3 months, chronic opioid agonist use, using immunosuppressive drugs, pregnant, inability to read a computer screen and use a mouse, and those currently taking LDN

75

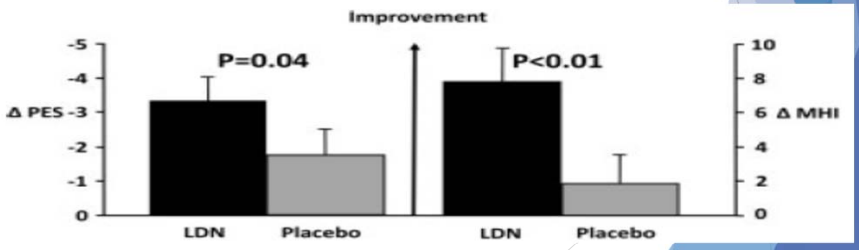
Adverse effects

- Vivid dreams were the most prominent adverse effect
- Others included fatigue, loss of appetite, and a sinus infection
- Euphoria was not reported as an adverse effect
- Serious adverse effects were not reported

76

Results

- Improvement in all mental health measures of the MSQLI
- No effect on the physical measures
- 3.3-point increase in mental component summary after 8 weeks LDN
  - Clinically relevant

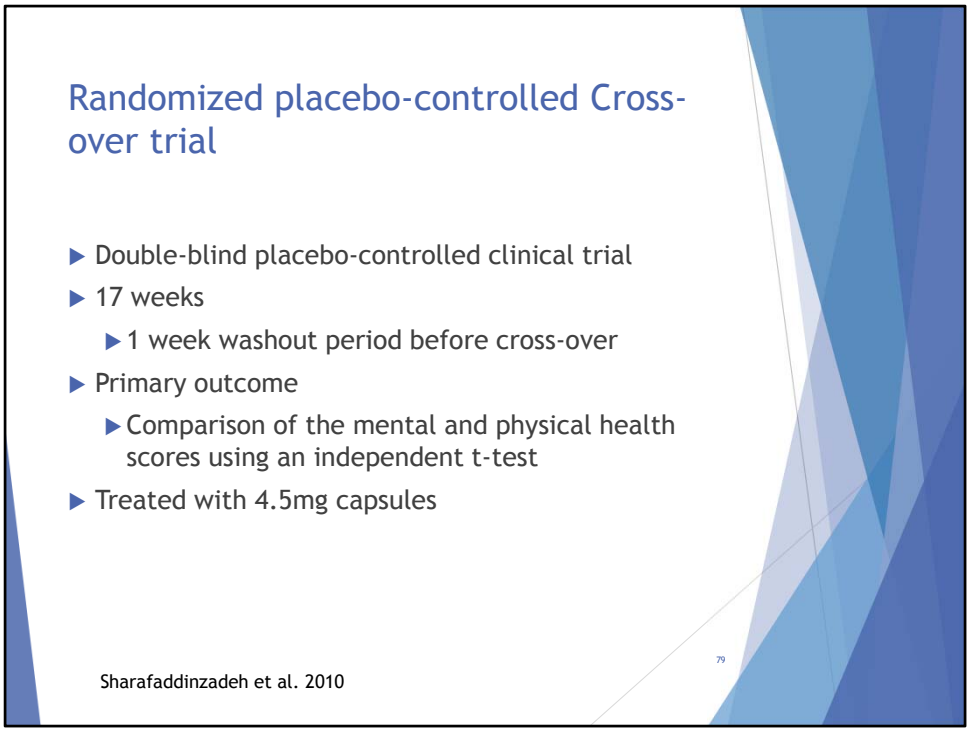


Clinically relevant because natalizumab was used in a RCT for 2 years and showed a 1-2.5 point increase in this mental component summary of the SF-36.
Rudick RA, Miller D, Hass S, et al, AFFIRM and SENTINEL Investigators.
Health related quality of life in multiple sclerosis:
effects of natalizumab. Ann Neurol 2007;62:335–346.

Summary

- 8 weeks of LDN was associated with symptomatic improvement in mental health
- Side effects were minimal
- Trial was performed at a single-center
- Further studies at multiple centers should be performed
  - Longer trials are necessary to determine the potential physical health benefits

78



This trial is somewhat similar to the one you already have in your slides. This article is a little more recent, has more patients, only showed significant difference in health perception. Still need more data to determine clinical significance and efficacy.

Found another article related to this. However, it is on mice with EAE but looks at LDN and OGF-OGFr and how it inhibits proliferation of B and T cells. I have this article saved if you'd like some slides made.

Subjects

- N= 96
- Relapsing-remitting or secondary progressive MS
- 15-65 years old
- Had the disease for greater than 6 months
- Exclusions
  - Chronic opioid agonist or immunosuppressant use

Sharafaddinzadeh et al. 2010

results

Table 3. Comparing characteristics of patients in two groups at week 8

Variable	Total patients ($n = 96$)	Group A ($n = 50$)	Group B ($n = 46$)	p-value between group A and B
Mental health composite score (mean ± SD)	58.04 ± 20.27	56.20 ± 21.45	60.03 ± 18.93	0.783
Physical health composite score (mean ± SD)	55.05 ± 18.98	53.59 ± 17.17	56.64 ± 20.84	0.208
Health perception (mean ± SD)	51.46 ± 20.00	46.20 ± 14.16	57.17 ± 23.70	0.006

Table 4. Comparing characteristics of patients in two groups at week 17

Variable	Total patients ($n = 96$)	Group A ($n = 50$)	Group B ($n = 46$)	p-value between group A and B
Mental health composite score (mean ± SD)	60.01 ± 19.01	61.65 ± 19.21	58.23 ± 18.83	0.238
Physical health composite score (mean ± SD)	55.80 ± 18.50	53.19 ± 16.28	58.64 ± 20.43	0.126
Health perception (mean ± SD)	52.14 ± 17.86	47.60 ± 15.33	57.07 ± 19.22	0.007

Grade I/II, disappeared after treatment-Nausea, headache, joint pain, mild irritability
No grade III/IV

Health perception was the only statistically different measure between the two groups. Significant before in middle and at end of trial.

- Based on 5 questions of physical health composite of the MSQoL-54 Questionaire

Responses to the questionnaire somewhat subjective

Summary

- Significant difference in health perception between placebo and LDN
- Several patients reported a benefit in bladder function
  - Decreased frequency or incontinence
- Safe option with minor side effects
- Needs trials with a longer duration or ultra-low dose naltrexone

82

Sharafaddinzadeh et al. 2010

Fibromyalgia

Fibromyalgia

- Symptoms include
  - Diffuse musculoskeletal pain
  - Increased sensitivity and tender points
  - Fatigue, sleep disturbance, cognitive impairment may worsen fibromyalgia

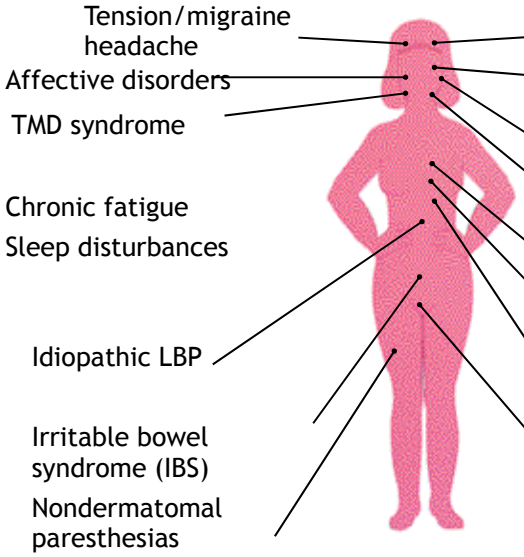
84

Fibromyalgia

- Affects 5% of women, 1.6% of men
- Most commonly diagnosed between 34 – 53 years
- Cause unknown
  - Possibly “central sensitivity syndrome” caused by proinflammatory cytokines

85

Related Symptoms and Syndromes



Aaron LA, et al. *Arch Intern Med.* 2000;160:221-227.

"Central Pain" Clinical Characteristics

- Multifocal pain (use pain diagram)
- Higher current and lifetime history of pain
- Multiple other somatic symptoms (fatigue, memory difficulties, sleep disturbances)
- Occurs over a wide continuum

(1) Ablin K, Clauw DJ. Rheum Dis Clin North Am 2009; 35(2):233-51.
(2) Wolfe F, et. al. J Rheumatol 2006; 33(11):2291-9.

"Central Pain" Clinical Characteristics

- 1.5 – 2X more common in females
- Strong familial/genetic underpinnings[1]
  - Take family history of pain
- Triggered or exacerbated by "stressors"[2]
- Generally normal physical examination except for diffuse tenderness and nonspecfiic neurological signs"[3]

(1) Kato K, et. al. Psychol Med 2008;1-9.
(2) Ablin K, Clauw DJ. Rheum Dis Clin North Am 2009; 35(2):233-51.
(3) Watson NF, et. al. Arthritis Rheum 2009; 60(9):2839-44.

Genetics of Fibromyalgia

- Familial predisposition[1]
  - Most recent work by Arnold, et al suggests >8 odds ratio (OR) for first-degree relatives, and much less familial aggregation (OR 2) with major mood disorders
  - Much stronger with bipolarity, obsessive compulsive disorder
- Genes that may be involved
  - 5-HT2A receptor polymorphism T/T phenotype[2]
  - Serotonin transporter[3]
  - Dopamine D4 receptor exon III repeat polymorphism[4]
  - COMT (catecholamine o-methyl transferase)[5]

1. Arnold et al. *Arthritis Rheum*. 2004;50:944-52. 2. Bondy et al. *Neurobiol Dis*. 1999;6:433-9.
3. Offenbaecher et al. *Arthritis Rheum*. 1999;42:2482-8. 4. Buskila et al. *Mol Psychiatry*. 2004;9:730-1.
5. Gürsoy et al. *Rheumatol Int*. 2003;23:104-7

Genetics of Pain

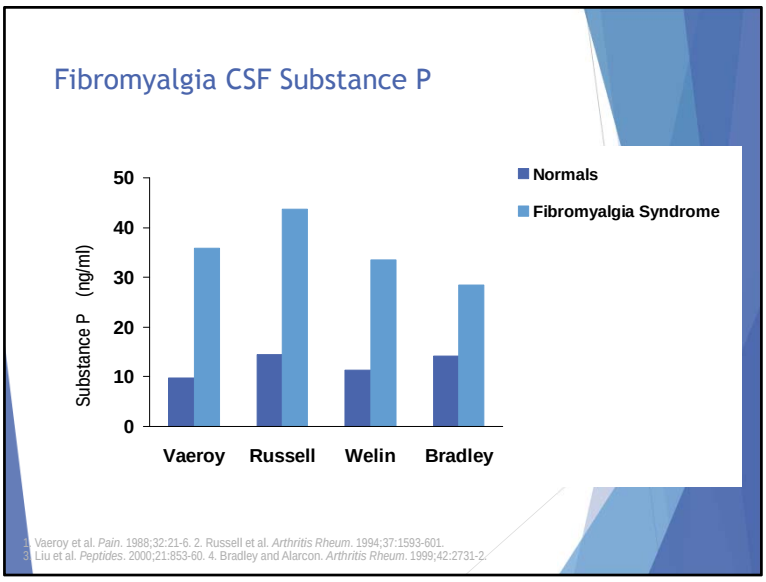
- Three specific genes have been shown to play major roles in pain sensitivity thus far:
  - A genetic mutation that leads to loss of function of the $Na_v1.7$ channel is associated with insensitivity to pain, whereas mutations (1.8, 1.9) that lead to increased function leads to erythromelalgia or paroxysmal extreme pain disorder[1]
  - GTP cyclohydrolase 1 (GCH1)[2]
  - Catechol-O-methyltranferase (COMT)[3]

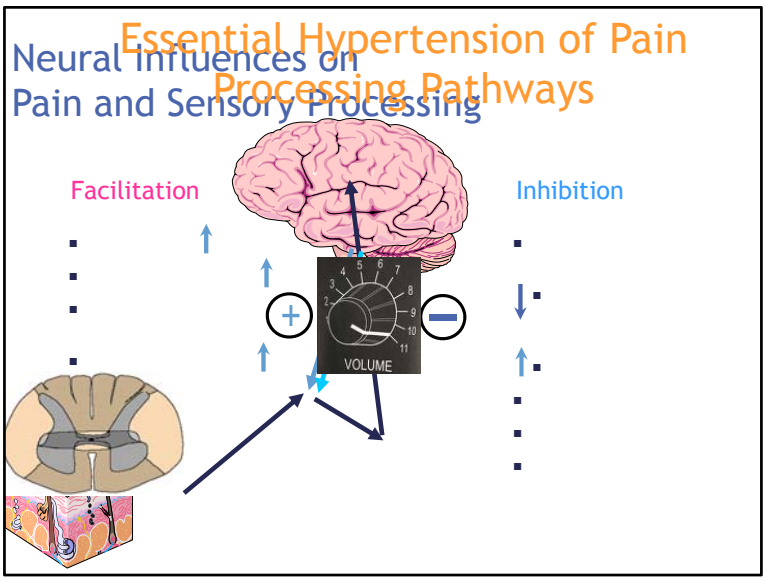
1. Amaya et. al. J Neuroscience 2006;26(50):12852-60.
2. Tegeder et.al., NatMed. 2006;12(11):1269-77.
3. Diatchenko et. al. HumMolGenet. 2005;14(1):135-43.

"Stressors" as Triggers

- Early life stressors[1]
  - Children born in 1958 who had experienced a motor traffic accident or who were institutionalized were 1.5 – 2X more likely to have CWP 42 years later
- Peripheral pain syndromes (e.g. RA, SLE, osteoarthritis)[2]
- Physical trauma (automobile accidents)
- Certain catastrophic events
  - (War but not natural disasters)[3]
- Infections
- Psychological stress/distress

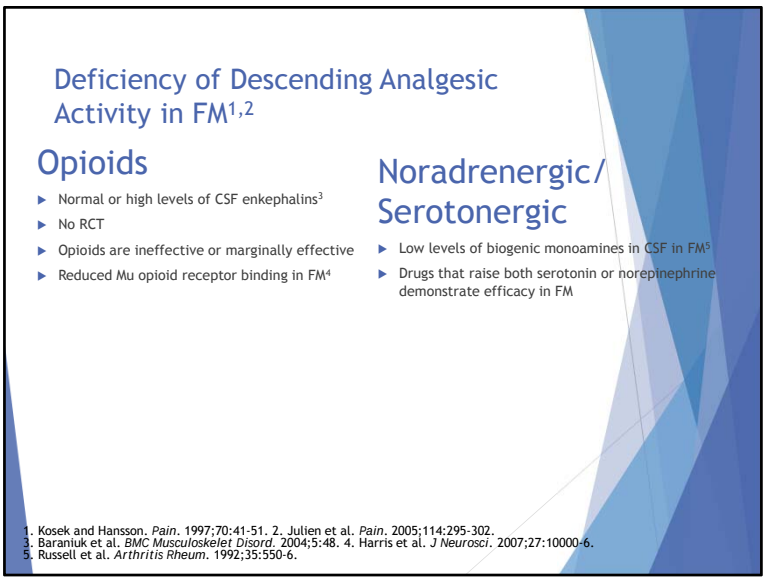
1. Jones et. al. 2007 ACR meeting. 2. Clauw et. al. JCR 1997.
3. Clauw et. al. J Occup Environ Med. 2003 Oct;45(10):1040-8.

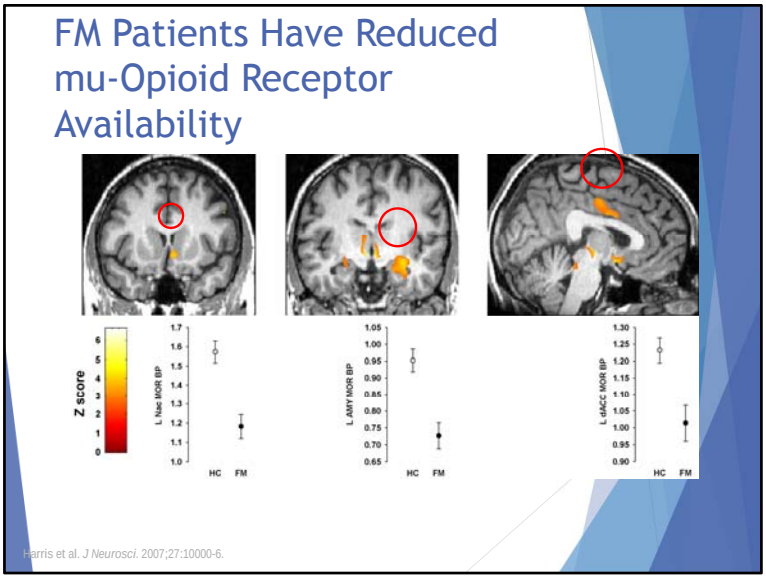

Fibromyalgia CSF Substance P
Substance P (ng/ml)
50
40
30
20
10
0
Vaeroy
Russell
Welin
Bradley
Normals
Fibromyalgia Syndrome
1. Vaeroy et al. Pain. 1988;32:21-6. 2. Russell et al. Arthritis Rheum. 1994;37:1593-601.
3. Liu et al. Peptides. 2000;21:853-60. 4. Bradley and Alarcon. Arthritis Rheum. 1999;42:2731-2.

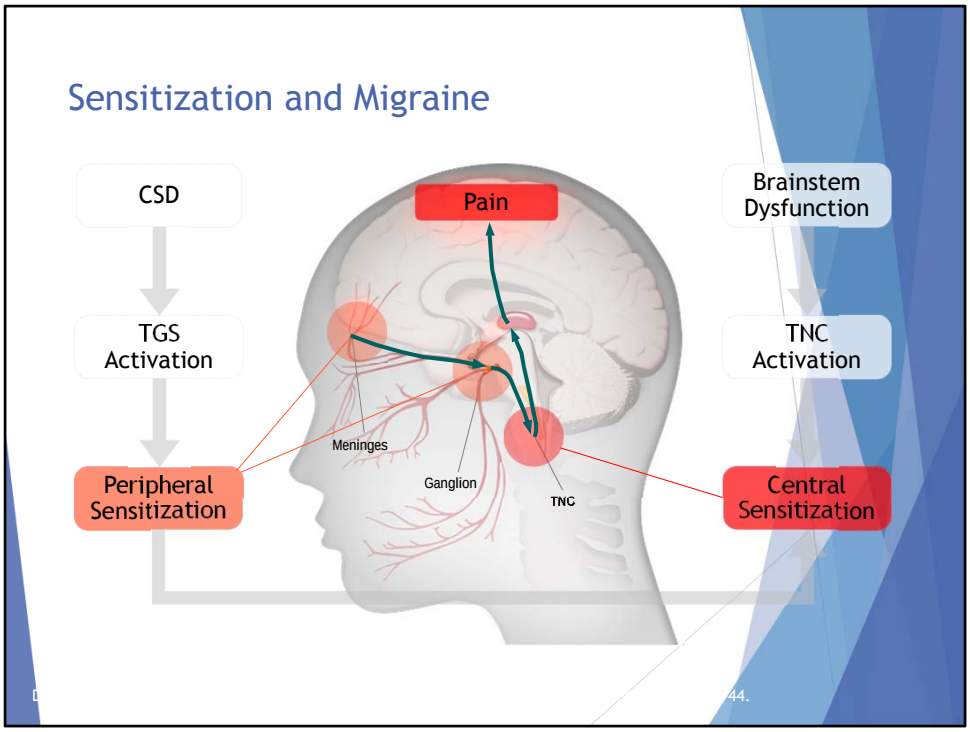


Recent studies have made it clear that an individual's "set point" or "volume control setting" for pain is set by a variety of factors, including the levels of neurotransmitters on the left that either facilitate pain transmission (turn up the gain or volume control) or those on the right that reduce pain transmission. Thus high levels of neurotransmitters on the left, or low levels of those on the right, would be capable of causing the diffuse hyperalgesia (increased volume control) seen in a variety of chronic pain states.

The arrows on this slide indicate the levels of these neurotransmitters in the cerebrospinal fluid (CSF) of individuals with fibromyalgia. You can see that there are high levels (2 – 3X than in healthy controls) of a number of neurotransmitters on the left, and low levels of one set of neurotransmitters (serotonin, norepinephrine, dopamine) on the right. The only neurotransmitter system that has been studied in FM and not shown to be abnormal in a direction that would cause hyperalgesia or an increased volume control is the opioidergic system, which seems to be appropriately increased in FM. This may help explain why opioidergic drugs do not seem to work very well for these central pain states such as FM.


Deficiency of Descending Analgesic Activity in FM[1,2]
Opioids
Normal or high levels of CSF enkephalins[3]
No RCT
Opioids are ineffective or marginally effective
Reduced Mu opioid receptor binding in FM[4]
Noradrenergic/ Serotonergic
Low levels of biogenic monoamines in CSF in FM[5]
Drugs that raise both serotonin or norepinephrine demonstrate efficacy in FM
1. Kosek and Hansson. Pain. 1997;70:41-51. 2. Julien et al. Pain. 2005;114:295-302.
3. Baraniuk et al. BMC Musculoskelet Disord. 2004;5:48. 4. Harris et al. J Neurosci. 2007;27:10000-6.
5. Russell et al. Arthritis Rheum. 1992;35:550-6.


FM Patients Have Reduced mu-Opioid Receptor Availability
Z score
L Nac MOR BP
L AMY MOR BP
L dACC MOR BP
HC
FM
Harris et al. J Neurosci. 2007;27:10000-6.



Goadsby, p 40,C2 Par 1, L 14-17

Dodick, p S182, Par 1, L 3-5

Dodick, p S189, C2 Par 1, L 7-9

Key point: Both TGS activation and brainstem dysfunction could contribute to central sensitization, which can lead to the perpetuation of the migraine process.

R1, p S183, C 2, Par Cont, L 11-14

Sensitization is the process whereby the stimulus needed to generate a response decreases over time, while the amplitude of the response to any given stimulus increases.[1]

R1, p S183, C 2, Par Cont, L 14-16

R1, p S183, C 2, Par 1, L 6-7

Peripheral sensitization refers to this process as it occurs in neurons of the peripheral nervous system[1]; peripheral sensitization has been proposed to be caused by the neuroinflammation of the dural and meningeal trigeminal nociceptors.[1]

R1, p S183, C 2, Par Cont, L 16-18

R1, p S183, C 2, Par 2, L 1-8

Central sensitization refers to the analogous process that occurs in the central nervous system.[1] In migraine, central sensitization is associated with abnormal neuronal excitability in the TNC.[1]

R1, p S183, C 2, Par 2, L 1-7

Peripheral sensitization could contribute to central sensitization, because an escalating barrage of input from sensitized trigeminal primary afferents may enhance TNC hyperexcitability.[1]

R2, p 40, C 2, Par 2, L 21-24

On the other hand, central sensitization may be a form of disinhibitory sensitization directly resulting from dysfunction of descending modulatory pathways within the brainstem and midbrain areas.[2]

R1, p S189, C2, Par 1, L 7-9

Central sensitization is likely to play a key role in maintaining the prolonged pain of migraine headache.

R1, p S182, C1, Para1, L6-10

References:

1. Dodick D, Silberstein S. Central sensitization theory of migraine: clinical implications. *Headache*. 2006;46(suppl 4):S182–S191.
2. Goadsby PJ. Recent advances in understanding migraine mechanisms, molecules and therapeutics. *Trends Mol Med*. 2007;13(1):39–44.

Central sensitization could also contribute to chronification of migraine.

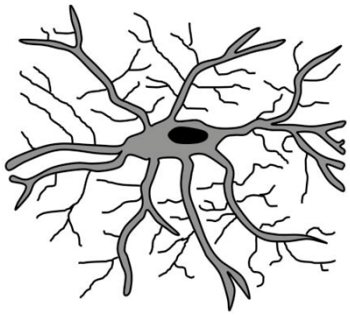
Migraine Explained

"You are genetically predisposed to migraine because of abnormal hyperexcitability of neurons in certain regions of the brain. We believe that this hyperexcitability is caused in part by mutations in channels on the surface of neurons that, when triggered, allow for the abnormal flow of sodium, calcium and other brain chemicals in and out of the cell. The hyperexcitable trigeminal nerve cells then send out impulses to the blood vessels in the brain and release substances that cause inflammation and swelling of the blood vessels resulting in pain and throbbing..."

(Evans & Evans, 2009)

Mechanism in Pain

- Naltrexone found to suppress microglia cells of the CNS
  - Decreases production of proinflammatory cytokines and neurotoxic superoxides



98

Microglia: migratory and act as phagocytes of waste products of the nervous system

Fibromyalgia pilot Study

- Single blind, placebo controlled, crossover
- Patients must meet American College of Rheumatology criteria for fibromyalgia

99

Fibromyalgia pilot Study

- Patients not told when they would receive placebo
  - Baseline: 2 weeks
  - Placebo: 2 weeks
  - LDN: 8 weeks
  - Washout: 2 weeks
- Naltrexone 4.5 mg and placebo used

100

Outcomes measured

- Primary outcome
  - Daily, self-reported assessment of symptom severity
- Secondary outcomes
  - Average daily pain
  - Highest pain
  - Fatigue
  - Sadness
  - Stress
  - Sleep quality
  - Ability to think and remember
  - GI symptoms
  - Headaches

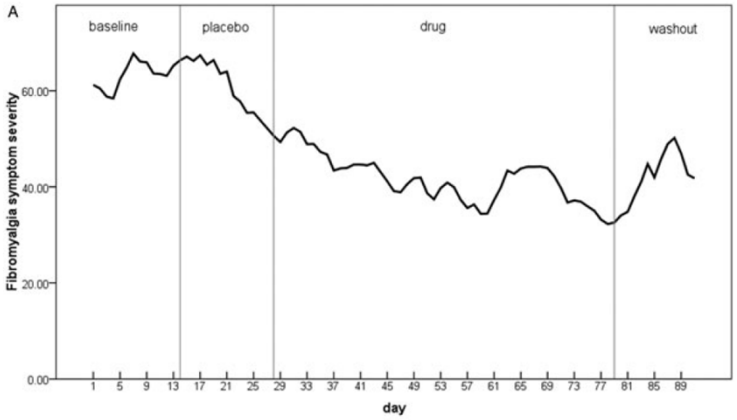
101

Baseline

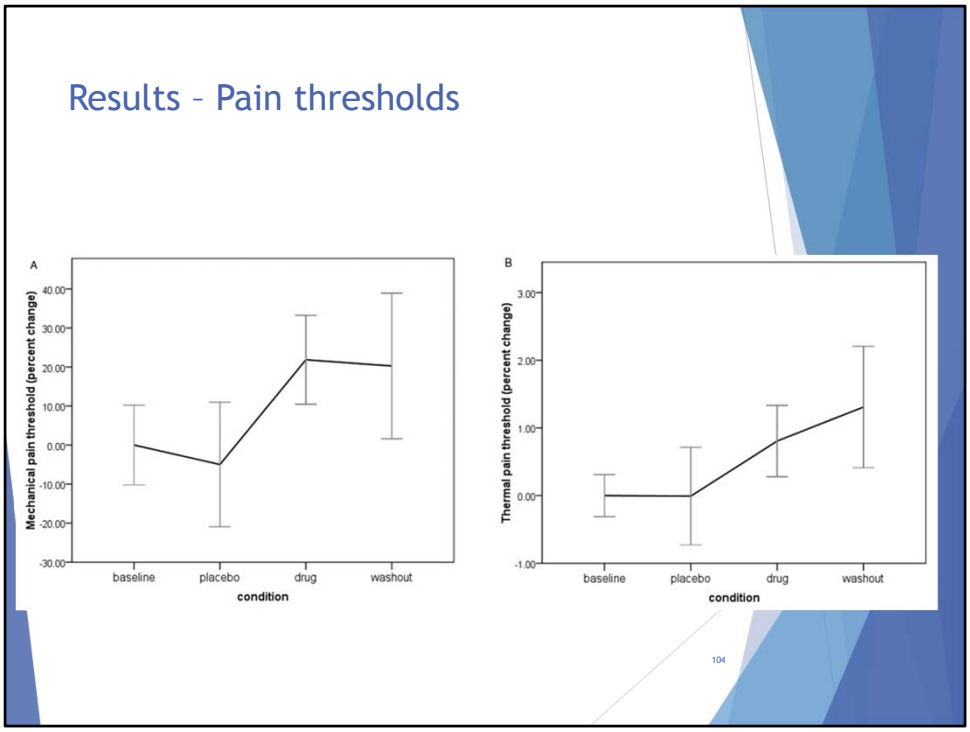
- N = 10
- Concomitant drugs allowed, except for opioids
  - Pregabalin
  - Duloxetine
  - Fluoxetine
  - Gabapentin
  - Cyclobenzaprine
  - Nortriptyline
- Average Fibromyalgia Impact questionnaire score
  - 67.2 +/- 15 (moderately severe symptoms)

102

Results



Drug decreased symptoms 32.5%
Pb decreased symptoms 2.3%
Responders: n = 6; 30% greater dec than pb
Drug also had significant affect on: daily pain, highest pain, fatigue, stress; not significant for the other 2ndary outcomes



Thermal pain: baseline 37.9C, drug incr 0.9C, pb no change
Cold pain: baseline 17.9C, no change in drug or pb
Mechanical pain: baseline 1.02 kg/cm-2, drug incr 0.22 kg, pb dec 0.07 kg

Discussion

- Pilot study shows significant benefit in fibromyalgia symptoms
- Time to peak effect: 28 days
- Mild side effects
  - N = 1: nausea and insomnia that resolved after a few nights
- Highest response seen in those with highest baseline ESR
- Possible risk of increased infection from decreased microglia activity

105

LDN Study & FIbromyalgia

- N=31
- Females
- Met fibromyalgia criteria
- Randomized, DB, PC, Counterbalanced, Crossover study
- Placebo
- LDN 4.5mg daily

106

LDN & Fibromyalgia

- Primary outcome
  - daily self-reported pain
- Secondary outcomes
  - general satisfaction with life,
  - positive mood
  - sleep quality
  - fatigue

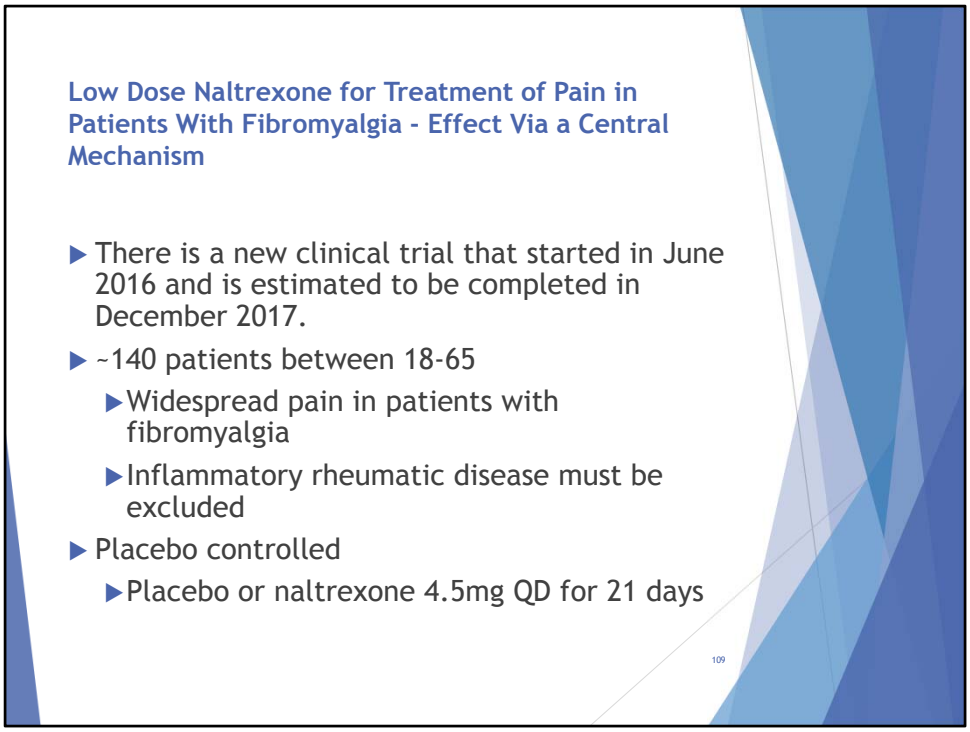
107

LDN & fibromyalgia

- 29% reduction in pain scores vs. 18 in placebo P=0.016
- General satisfaction with life and mood were improved
- Fatigue and sleep not improved
- Well tolerated and SE similar to placebo

Younger et al. Arthritis Rheum. 2013 Feb;65(2):529-38. doi: 10.1002/art.37734

108



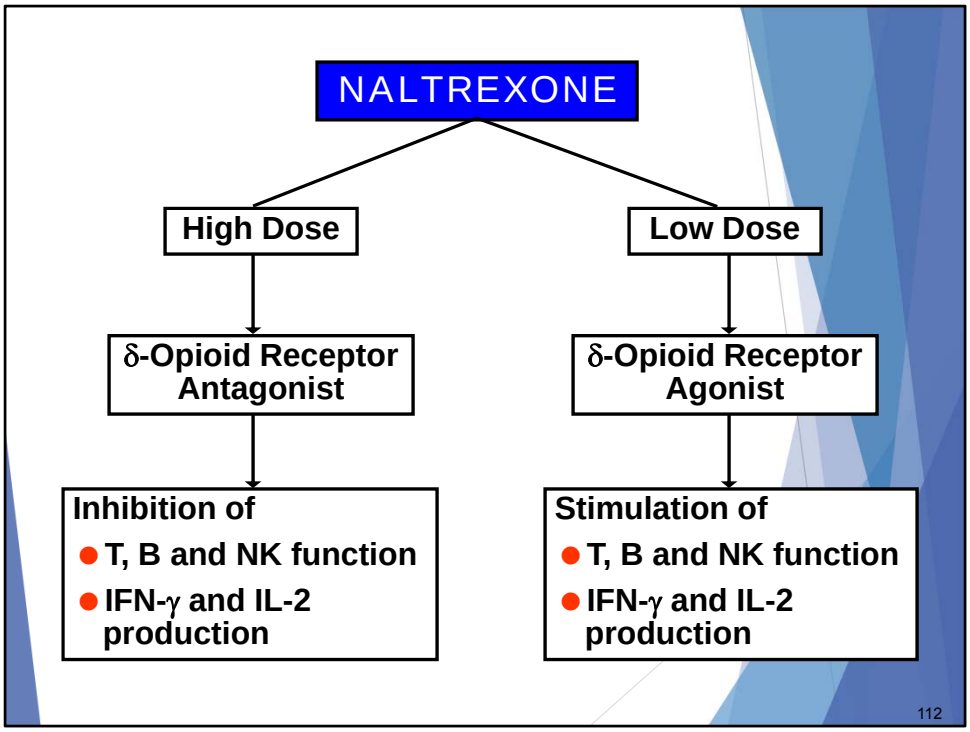
https://clinicaltrials.gov/ct2/show/NCT02806440

Chronic Pain

Mechanism in Chronic Pain

- Patients on opioids for chronic pain develop tolerance
  - Due to stimulation of opioid receptors which cause an opposite effect on cells
- Ultralow-dose naltrexone would interrupt antagonistic signaling

111


NALTREXONE
High Dose
Low Dose
δ-Opioid Receptor Antagonist
δ-Opioid Receptor Agonist
Inhibition of
T, B and NK function
IFN-γ and IL-2 production
Stimulation of
T, B and NK function
IFN-γ and IL-2 production
112

Randomized, Double-Blind, Placebo-Controlled, Counterbalanced, Crossover Trial

- Subjects
  - Women 18-65
- Exclusions:
  - Evidence of joint inflammation or reported any history of rheumatic or autoimmune disease
  - Those taking opioid analgesic
  - Have been on the same medication for 2 months

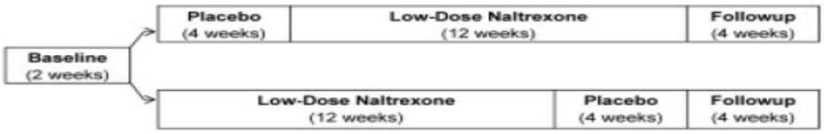


Figure 1. Outline of the study protocol.

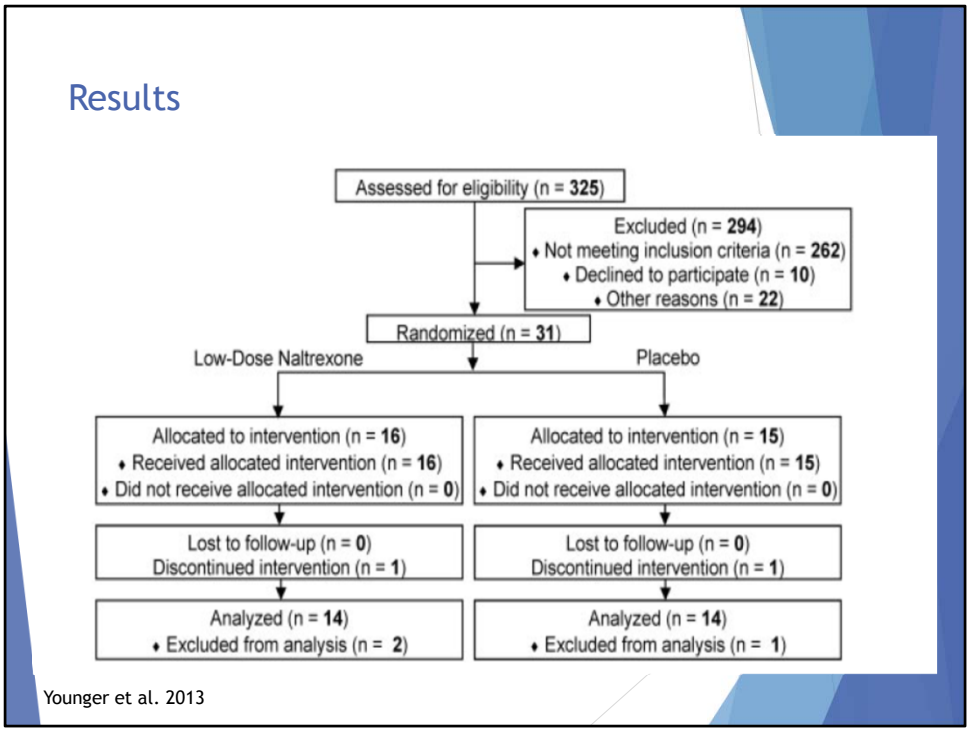
Younger et al. 2013

"Participants also submitted a blood sample at the screening visit and were excluded from further participation if the following thresholds were met: rheumatoid factor (RF) 20 IU/ml, antinuclear antibody (ANA) titer 1:80, erythrocyte sedimentation rate (ESR) 60 mm/ hour, or C-reactive protein (CRP) level 2 mg/dl. Individuals presenting with significant psychiatric distress or a score of 29 on the revised Beck Depression Inventory (BDI-II) were excluded from the study." (Younger et al. 2013)

Treatment

- 4.5mg naltrexone
  - PO one hour before bedtime
- Placebo
  - Microcrystalline filler and sweetener
  - PO one hour before bedtime
- Daily Assessment
  - Participants completed daily symptom reports using a Palm Z22 handheld computer at bedtime
- Primary Outcome - “how severe has your pain been today on a scale 0-100”
- Secondary Outcome - life satisfaction, mood, sleep quality, and fatigue.

Younger et al. 2013



Study design flow chart

Results

Table 2. Change in daily pain scores (primary outcome variable), by treatment group*

Study group	Pain score at baseline	Change in pain score with treatment: Placebo	Change in pain score with treatment: Low-dose naltrexone
Placebo first	50.0	−10.7 (−19.4)	−16.6 (−31.5)
Low-dose naltrexone first	51.5	−11.7 (−16.5)	−14.3 (−26.0)
All subjects	50.8	−11.2 (−18.0)	−15.5 (−28.8)

Table 3. Reported side effects, by treatment group*

Side effect	Placebo	Low-dose naltrexone
Vivid dreams	13	37†
Headache	3	16‡
Nausea/upset stomach	7	16
Nightmares	3	13
Insomnia	10	16
Dry mouth or dry throat	3	10
Shortness of breath	0	3
Anxiety	0	3
Agitation	0	3
Increased hair growth	0	3
Increased sweating	0	3
Weight gain	3	0
Dizziness	3	3

* Values are the percentage of participants reporting each side effect.
† $\chi^2 = 4.36$, $P = 0.037$.
‡ $\chi^2 = 4.05$, $P = 0.044$.

Younger et al. 2013

"At the end of the low-dose naltrexone condition, pain was reduced by 28.8 9.3%. The difference in pain reduction between placebo and low-dose naltrexone was significant (F[1,30] 6.4, *P* 0.016). There was no significant main effect for assignment in the placebo-first versus the low-dose naltrexone–first group (F[1,26] 0.1, *P* 0.710) and there was no condition group interaction (F[1,34] 0.02, *P* 0.899)."

Only two side effects, vivid dreams (2 4.4, *P* 0.037) and headache (2 4.05, *P* 0.044), were more frequently reported in the low-dose naltrexone condition.

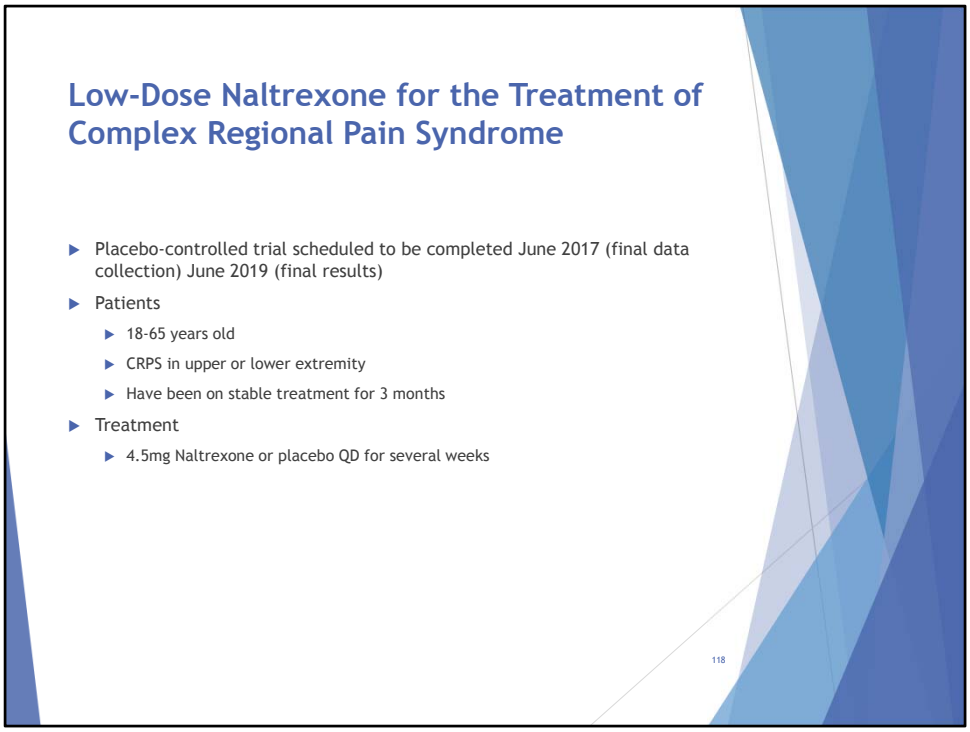
Mood and satisfaction with life were the only two secondary outcomes that were significant

summary

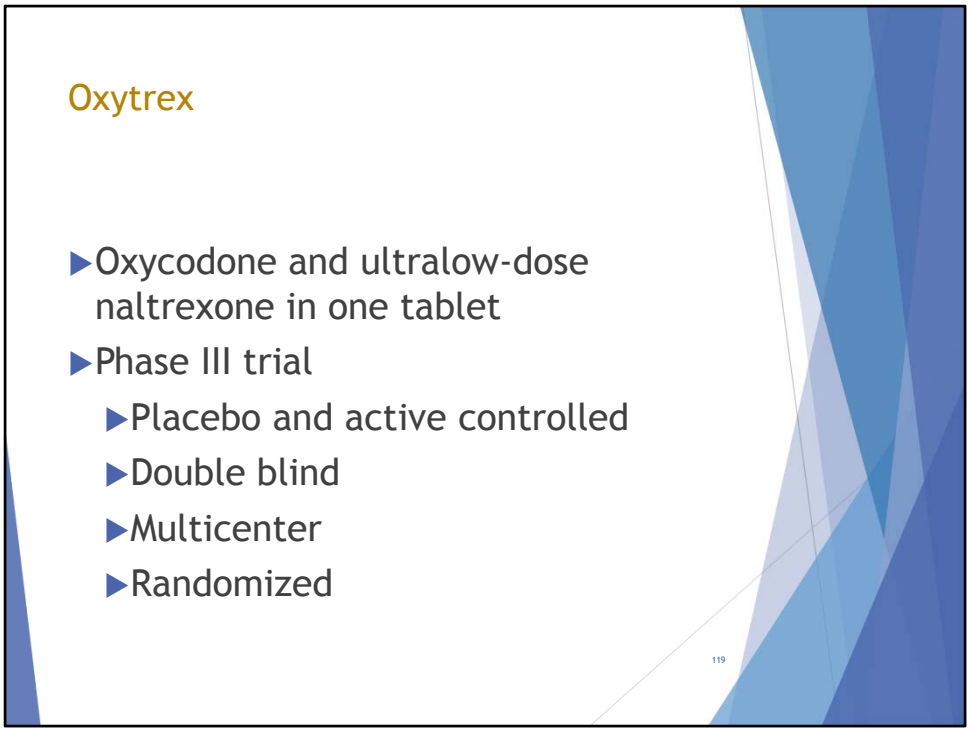
- Data show low dose naltrexone reduces pain associated with fibromyalgia
  - 28.8% average reduction in pain
    - Similar to the 32.5% seen in previous Younger et al. study
- Well tolerated
  - Vivid dreams and headaches were the only significant side effects
- Again, widely available and inexpensive
- Future investigations
  - Parallel, randomized controlled trials

117

Younger et al. 2013

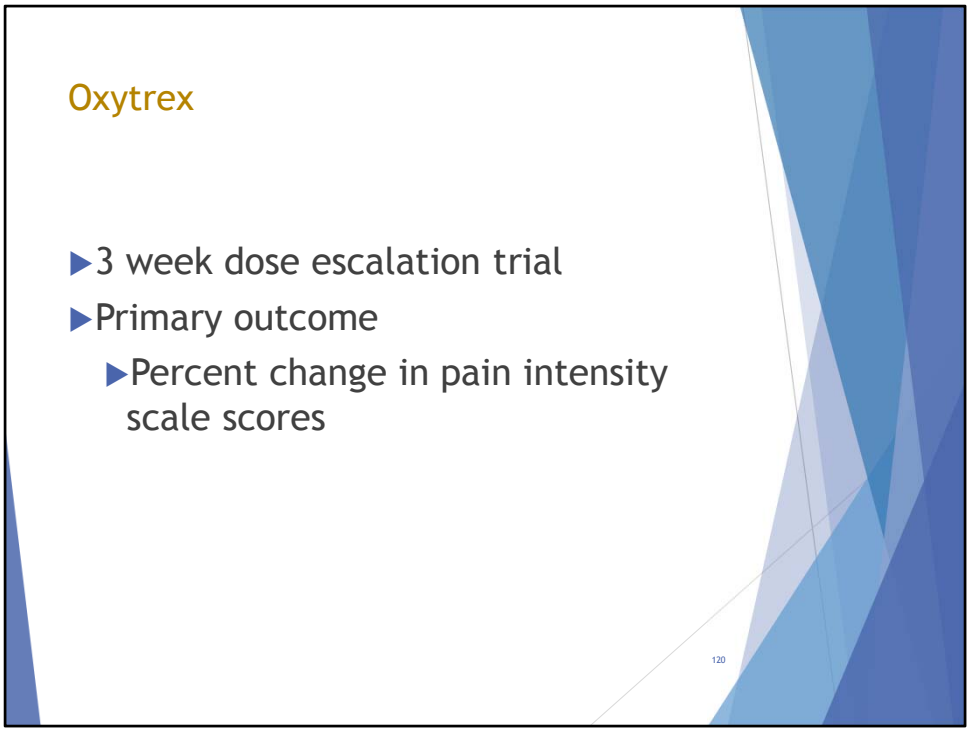


https://clinicaltrials.gov/ct2/show/NCT02502162



11-point numeric
diary Pain Intensity Scale
Pick 0 (no pain) -10 (severe pain)

Other efficacy assessments, conducted weekly, included
(1) quality of analgesia: patients rated pain relief as poor, fair, good, very good, or excellent
(2) pain control: controlled for a few hours or less each day, several hours each day, most of each day, or throughout each day
(3) global assessment of study drug: poor, fair, good, very good, or excellent, of well-being in this evaluation. taking into consideration the quality of pain relief, side effects, activity level, mood, and sense
In addition, responses to the SF-12 Health Survey11 and the Western Ontario and MacMaster Universities(WOMAC) Osteoarthritis Index



11-point numeric
diary Pain Intensity Scale
Pick 0 (no pain) -10 (severe pain)

Other efficacy assessments, conducted weekly, included
(1) quality of analgesia: patients rated pain relief as poor, fair, good, very good, or excellent
(2) pain control: controlled for a few hours or less each day, several hours each day, most of each day, or throughout each day
(3) global assessment of study drug: poor, fair, good, very good, or excellent, of well-being in this evaluation. taking into consideration the quality of pain relief, side effects, activity level, mood, and sense
In addition, responses to the SF-12 Health Survey11 and the Western Ontario and MacMaster Universities(WOMAC) Osteoarthritis Index

Phase II Baseline

- N = 360 patients with osteoarthritis (OA) of knee or hip
- 4 treatment groups (1:2:2:2 ratio)
  - Placebo
  - Oxycodone QID
  - Oxytrex BID
  - Oxytrex QID

121

Results

Table 3. Pain Intensity Scores (Mean ± Standard Deviation)

	Placebo	Oxycodone QID	Oxytrex QID	Oxytrex BID
Baseline	7.7 ± 1.3	7.4 ± 1.3	7.7 ± 1.4	7.6 ± 1.4
Week 1	6.5 ± 2.1	6.1 ± 2.2	6.3 ± 2.1	5.5 ± 2.1*
Week 2	6.2 ± 2.5	5.8 ± 2.3	6.0 ± 2.2	5.0 ± 2.2†
Week 3	6.1 ± 2.8	5.6 ± 2.3	5.7 ± 2.4	4.5 ± 2.4‡

Abbreviations: qid, 4 times a day; bid, twice a day.
*P = .01 vs. placebo.
†P = .002 vs placebo and P = .05 vs oxycodone.
‡P < .0001 vs placebo and P = .009 vs oxycodone.

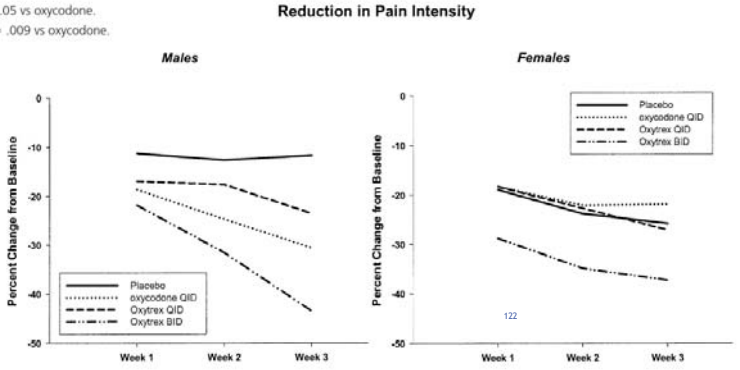
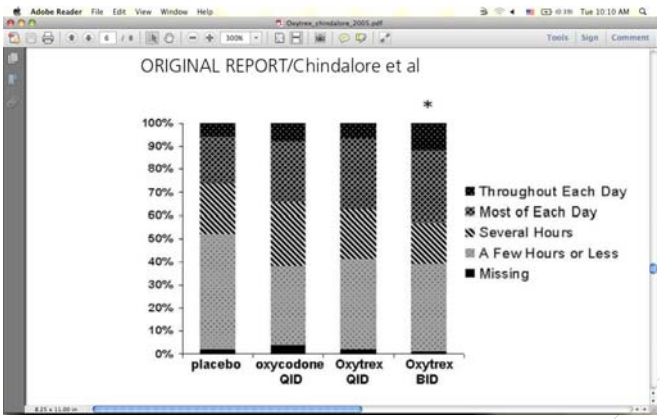


Table 3- shows pain scores decreasing in all groups
Figure- separates pain into male and female, males had better response

Results



123

Week 3: pain control throughout the day pain was controlled throughout each day or most of each day were 26.0% for placebo, 34.3% for oxycodone, 37.3
for Oxytrex qid, and 43.2% for Oxytrex bid
Oxytrex bid was the only group significantly better than placebo at week 3 (P .05).

Summary of Oxytrex

- Most common side effects: nausea, constipation, dizziness
  - All greater than placebo
- Oxytrex QID vs. Oxytrex BID
  - Same dose of oxycodone, different dose naltrexone
  - BID regimen was more effective
  - Possibly naltrexone in QID dosing was too high

124

Summary of Oxytrex

- Naltrexone enhanced and prolonged analgesia of oxycodone
  - Reduces the rewarding effect of opioids but also prevents withdrawal symptoms
  - Be careful in patients on long term opioids as may precipitate withdrawal

125

LDN and its prevention of morphine induced adverse events

- 14 patients with chronic nonmalignant pain
  - Received intrathecal morphine
- 15 patients with cancer pain
  - Received oral morphine
- Adverse effect intensity was measured on a 0-4 scale
- Pain measured using a 10cm visual analog scale
- Patients received 1mg of NTX 1 hour before morphine

126

Results

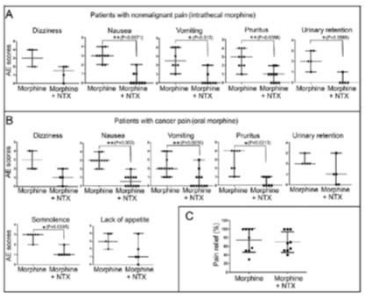
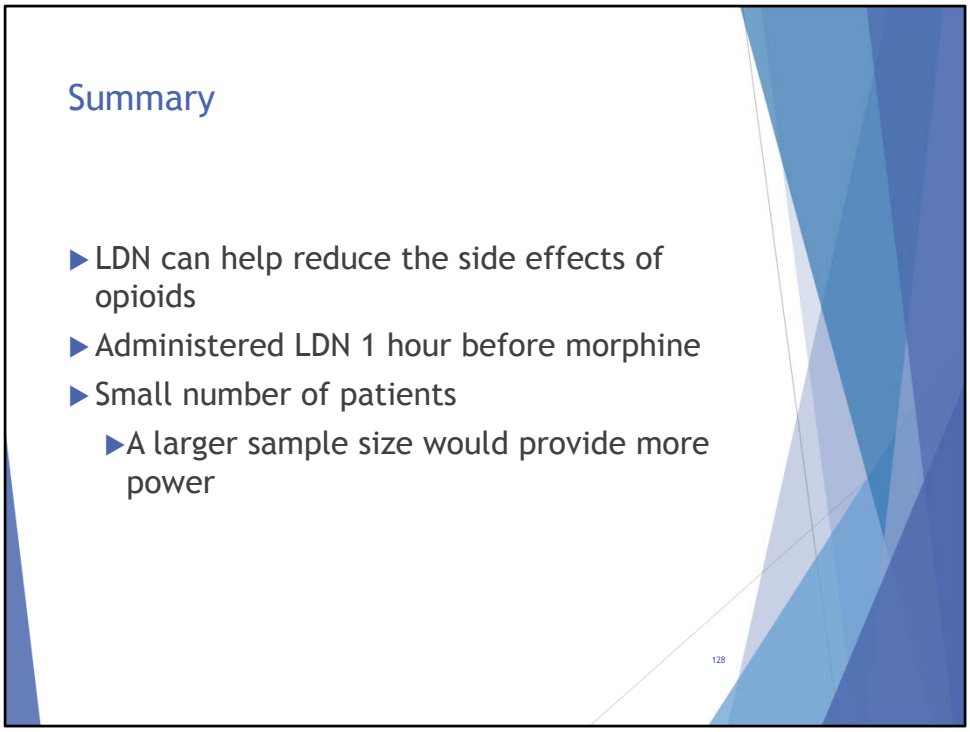


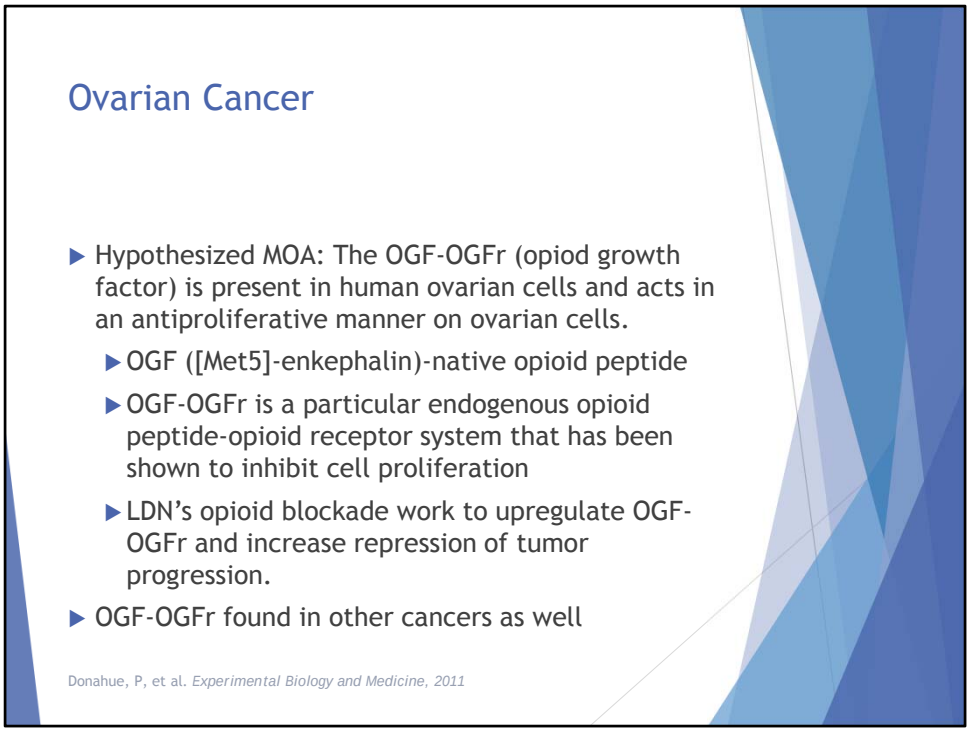
Figure 1 Dot plots showing, for each AE, the median score values with ranges calculated on patient with nonmalignant pain (A) and on patients with cancer pain (B) after treatment with morphine alone and after treatment with morphine plus NTX. Statistical analysis was performed using the two-tailed Wilcoxon matched-pairs signed-rank test. One asterisk (*) indicates a significant difference ($P < 0.05$) and two asterisks (**) indicates a very significant difference ($P < 0.01$). Actual P values are also reported for all significant differences. + indicates a P value approaching statistical significance ($P = 0.0568$). (C) Dot plots reporting the means and standard deviations of pain relief percentages calculated from VAS data on patients with nonmalignant or cancer pain after treatment with morphine alone and with morphine plus NTX. NTX treatment did not significantly reduce morphine analgesic efficacy, as evaluated by Student *t*-test.

127

Pretreatment with LDN reduced intensity of nausea, vomiting, and pruritis in non malignant pain
Reduced intensity for nausea, vomiting, pruritis, and somnolence in cancer pain
Trend of reduction for dizziness, urinary retention and lack of appetite (cancer pt only)
Previous studies show NTX dose less than 6mg did not reduce opioid analgesic effects



Some studies demonstrated similar effects while co-administering LDN with the opiate such as in your study with oxytrex on slide 96
Micromedex- LDN for prophylaxis of adverse effects when taking morphine- one study administered 6mg naltrexone 60 minutes after intrathecal morphine, second study administered 6mg of naltrexone 5 minutes before morphine epidural. Duration of analgesia was shorter when naltrexone was administered but there was a reduction in morphine related side effects.



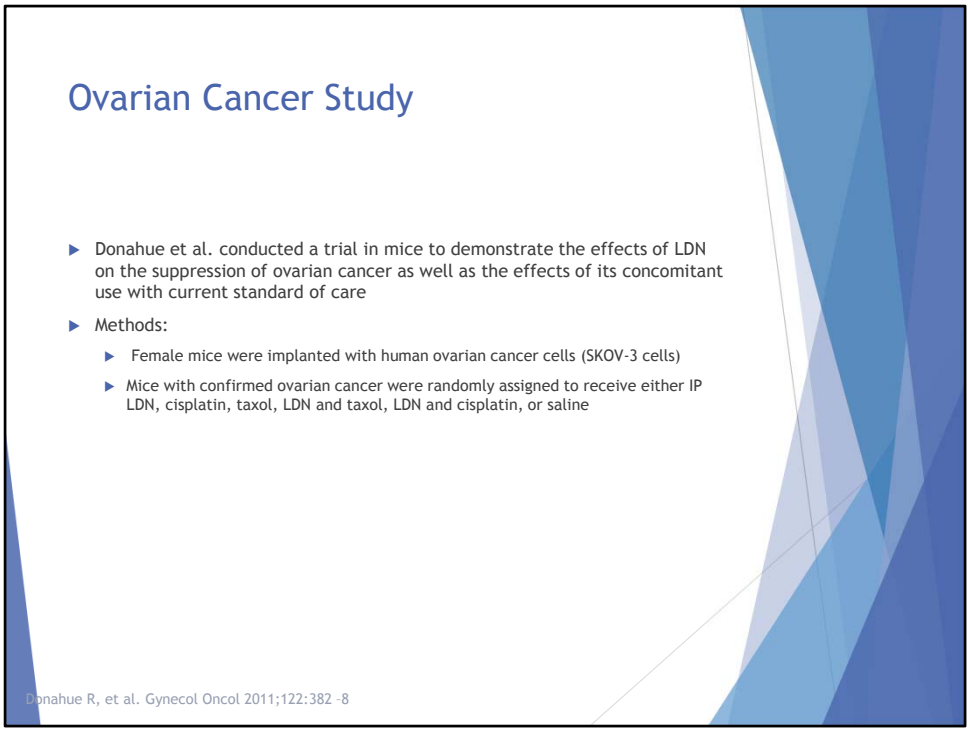
1. R. N. Donahue, P. J. McLaughlin, I. S. Zagon. Low-dose naltrexone suppresses ovarian cancer and exhibits enhanced inhibition in combination with cisplatin. *Experimental Biology and Medicine, 2011; DOI: 10.1258/ebm.2011.011096* (http://ebm.rsmjournals.com.proxy.lib.umich.edu/content/236/7/883.long)

Abstract: Ovarian cancer is the leading cause of death from gynecological malignancies. Although initial therapeutic modalities are successful, 65% of these women relapse with only palliative treatments available thereafter. Endogenous opioids repress the proliferation of human ovarian cancer cells in vitro, and do so in a receptor-mediated manner. The present study examined whether modulation of opioid systems by the opioid antagonist naltrexone (NTX), alone or in combination with standard of care therapies (taxol/paclitaxel, cisplatin), alters human ovarian cancer cell proliferation in tissue culture and tumor progression in mice. Administration of NTX for six hours every two days, but not continuously, reduced DNA synthesis and cell replication from vehicle-treated controls in tissue culture. Moreover, brief exposure to NTX in combination with taxol or cisplatin had an enhanced anticancer action. Mice with established ovarian tumors and treated with a low dosage of NTX (LDN), which invokes a short period of opioid receptor blockade, repressed tumor progression in a non-toxic fashion by reducing DNA synthesis and angiogenesis but not altering cell survival. The combination of LDN with cisplatin, but not taxol, resulted in an additive inhibitory effect on tumorigenesis with enhanced depression of DNA synthesis and angiogenesis. LDN combined with cisplatin alleviated the toxicity (e.g. weight loss) associated with cisplatin. LDN treatment upregulated the expression of the opioid growth factor (OGF, chemical term ([Met 5]-enkephalin) and its receptor, OGFr. Previous tissue culture studies have reported that OGF is the only opioid peptide with antiproliferative activity on ovarian cancer cells, with OGF action mediated by OGFr. Thus, the common denominator of intermittent opioid receptor blockade by short-term NTX or LDN on ovarian cancer proliferation and tumorigenesis recorded herein appears to be related to the OGF–OGFr axis. These preclinical data may offer a non-toxic and efficacious pathway-related treatment that can benefit patients with ovarian cancer

2, Chobanian N, Dietrick CS. Ovarian cancer. Surg Clin North Am 2008;88:285–99

3. Donahue RN, McLaughlin PJ, Zagon IS. The opioid growth factor (OGF)and low dose naltrexone (LDN) suppress human ovarian cancer progression in mice. Gynecol Oncol 2011;122:382 –8

One particular endogenous opioid peptide–opioid receptor system involved in growth modulation by NTX has been demonstrated to upregulate is the opioid growth factor (OGF) and its receptor, OGFr.9,28 OGF, chemically termed [Met5]-enkephalin, is a constitutively expressed native opioid peptide that is autocrine produced and secreted.29 OGF interacts with OGFr (a non-classical opioid receptor) to delay the G1/S phase of the cell cycle by modulating cyclin-dependent kinase inhibitory (CKI) pathways, and inhibits cell proliferation in normal and neoplastic cells, including ovarian cancer.5,6,29–32 The OGF–OGFr axis has been shown to be present in human ovarian cancer, with OGFr RNA, protein and binding activity documented in these cells in vitro,5 and OGF detected by radioimmunoassay in surgical samples taken from human ovarian neoplasms.33 Studies in tissue culture have documented that OGF is the only endogenous opioid peptide which regulates ovarian cancer cell proliferation,5 and that the inhibitory action of OGF is mediated by OGFr.5,6 An increase in OGF–OGFr activity in human ovarian cancer cells in tissue culture by the addition of exogenous OGF has been reported to markedly suppress cell proliferation in a non-toxic manner by targeting the CKI pathways.5,6 Moreover, continuous intervention of opioid peptide–opioid receptor interaction with the opioid antagonist NTX accelerates cell proliferation.5,6



1. R. N. Donahue, P. J. McLaughlin, I. S. Zagon. Low-dose naltrexone suppresses ovarian cancer and exhibits enhanced inhibition in combination with cisplatin. *Experimental Biology and Medicine, 2011; DOI: 10.1258/ebm.2011.011096* (http://ebm.rsmjournals.com.proxy.lib.umich.edu/content/236/7/883.long)

Abstract: Ovarian cancer is the leading cause of death from gynecological malignancies. Although initial therapeutic modalities are successful, 65% of these women relapse with only palliative treatments available thereafter. Endogenous opioids repress the proliferation of human ovarian cancer cells in vitro, and do so in a receptor-mediated manner. The present study examined whether modulation of opioid systems by the opioid antagonist naltrexone (NTX), alone or in combination with standard of care therapies (taxol/paclitaxel, cisplatin), alters human ovarian cancer cell proliferation in tissue culture and tumor progression in mice. Administration of NTX for six hours every two days, but not continuously, reduced DNA synthesis and cell replication from vehicle-treated controls in tissue culture. Moreover, brief exposure to NTX in combination with taxol or cisplatin had an enhanced anticancer action. Mice with established ovarian tumors and treated with a low dosage of NTX (LDN), which invokes a short period of opioid receptor blockade, repressed tumor progression in a non-toxic fashion by reducing DNA synthesis and angiogenesis but not altering cell survival. The combination of LDN with cisplatin, but not taxol, resulted in an additive inhibitory effect on tumorigenesis with enhanced depression of DNA synthesis and angiogenesis. LDN combined with cisplatin alleviated the toxicity (e.g. weight loss) associated with cisplatin. LDN treatment upregulated the expression of the opioid growth factor (OGF, chemical term ([Met 5]-enkephalin) and its receptor, OGFr. Previous tissue culture studies have reported that OGF is the only opioid peptide with antiproliferative activity on ovarian cancer cells, with OGF action mediated by OGFr. Thus, the common denominator of intermittent opioid receptor blockade by short-term NTX or LDN on ovarian cancer proliferation and tumorigenesis recorded herein appears to be related to the OGF–OGFr axis. These preclinical data may offer a non-toxic and efficacious pathway-related treatment that can benefit patients with ovarian cancer

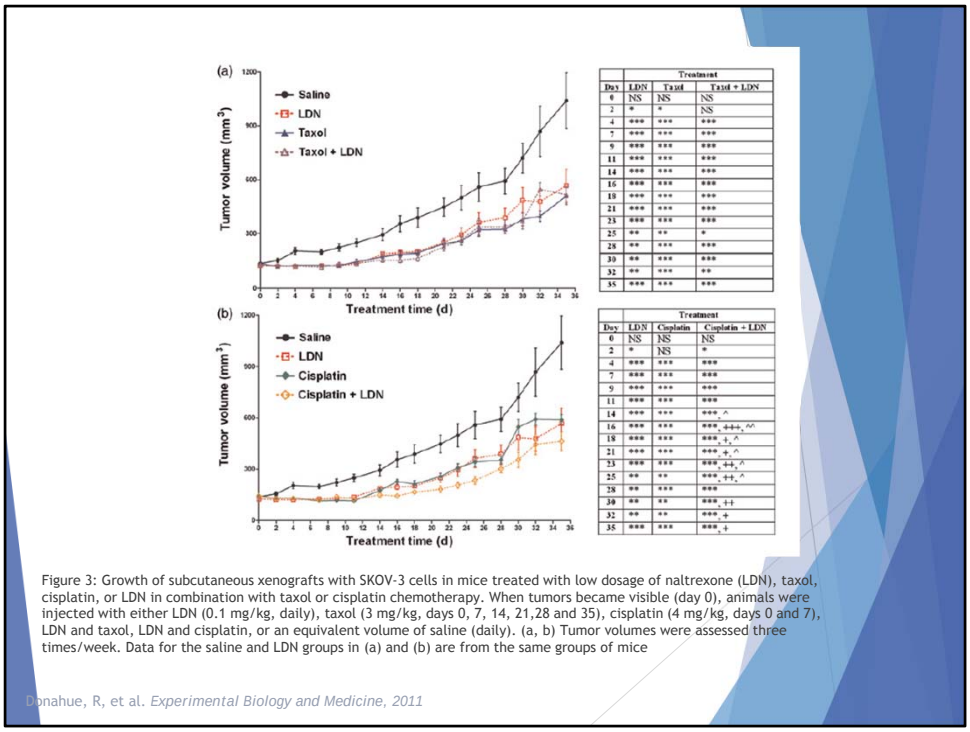
2, Chobanian N, Dietrick CS. Ovarian cancer. Surg Clin North Am 2008;88:285–99

3. Donahue RN, McLaughlin PJ, Zagon IS. The opioid growth factor (OGF)and low dose naltrexone (LDN) suppress human ovarian cancer progression in mice. Gynecol Oncol 2011;122:382 –8

Ovarian Cancer Study

- Results: “Mice with established ovarian tumors and treated with a low dosage of NTX (LDN), which invokes a short period of opioid receptor blockade, repressed tumor progression in a non-toxic fashion by reducing DNA synthesis and angiogenesis but not altering cell survival. The combination of LDN with cisplatin, but not taxol, resulted in an additive inhibitory effect on tumorgenesis with enhanced depression of DNA synthesis and angiogenesis. LDN combined with cisplatin alleviated the toxicity (e.g. weight loss) associated with cisplatin.”

Donahue R, et al. Gynecol Oncol 2011;122:382 -8



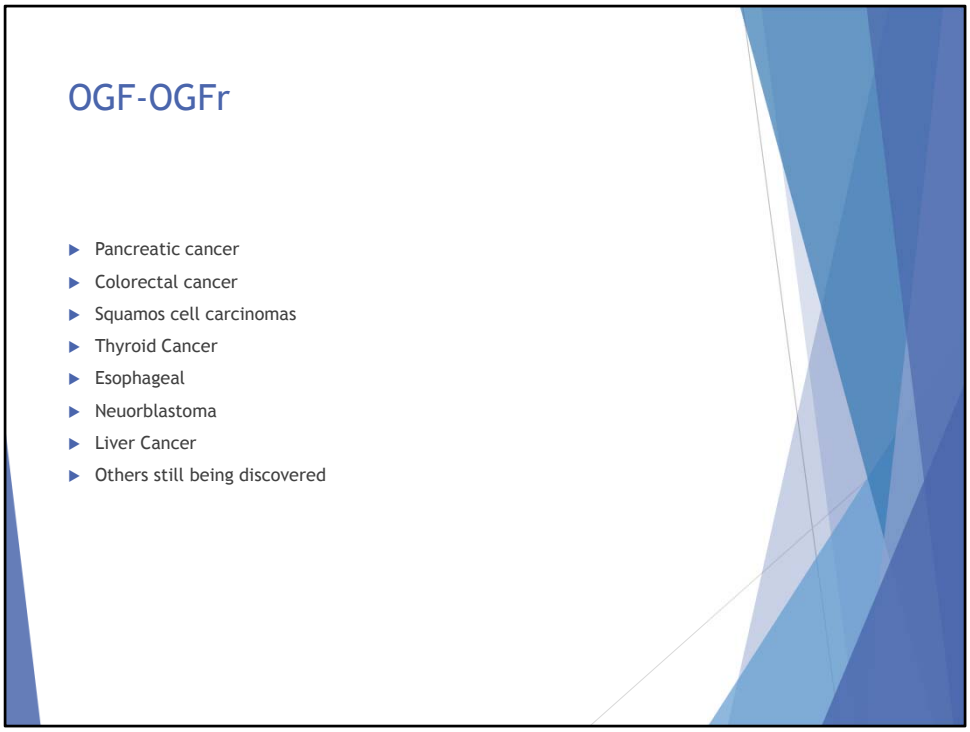
	Treatment		
Day	LDN	Taxol	Taxol + LDN
0	NS	NS	NS
2	*	*	NS
4	***	***	***
7	***	***	***
9	***	***	***
11	***	***	***
14	***	***	***
16	***	***	***
18	***	***	***
21	***	***	***
23	***	***	***
25	**	**	*
28	**	***	***
30	**	***	***
32	**	***	**
35	***	***	***

	Treatment		
Day	LDN	Cisplatin	Cisplatin + LDN
0	NS	NS	NS
2	*	NS	*
4	***	***	***
7	***	***	***
9	***	***	***
11	***	***	***
14	***	***	*** ^
16	***	***	*** ++, ^^
18	***	***	*** +, ^
21	***	***	*** +, ^
23	***	***	*** ++, ^
25	**	**	*** ++, ^
28	**	***	***
30	**	**	*** ++
32	**	**	*** +
35	***	***	*** +

Figure 3: Growth of subcutaneous xenografts with SKOV-3 cells in mice treated with low dosage of naltrexone (LDN), taxol, cisplatin, or LDN in combination with taxol or cisplatin chemotherapy. When tumors became visible (day 0), animals were injected with either LDN (0.1 mg/kg, daily), taxol (3 mg/kg, days 0, 7, 14, 21,28 and 35), cisplatin (4 mg/kg, days 0 and 7), LDN and taxol, LDN and cisplatin, or an equivalent volume of saline (daily). (a, b) Tumor volumes were assessed three times/week. Data for the saline and LDN groups in (a) and (b) are from the same groups of mice

Donahue, R, et al. *Experimental Biology and Medicine, 2011*

1. R. N. Donahue, P. J. McLaughlin, I. S. Zagon. Low-dose naltrexone suppresses ovarian cancer and exhibits enhanced inhibition in combination with cisplatin. *Experimental Biology and Medicine, 2011; DOI: 10.1258/ebm.2011.011096* (http://ebm.rsmjournals.com.proxy.lib.umich.edu/content/236/7/883.long)



1. Donahue RN, McLaughlin PJ, Zagon IS. long Low-dose naltrexone targets the opioid growth factor-opioid growth factor receptor pathway to inhibit cell proliferation: mechanistic evidence from a tissue culture model. Exp Biol Med (Maywood). 2011 Sep 1;236(9):1036-50. doi: (http://ebm.rsmjournals.com.proxy.lib.umich.edu/content/236/9/1036)

Naltrexone (NTX) is an opioid antagonist that inhibits or accelerates cell proliferation in vivo when utilized in a low (LDN) or high (HDN) dose, respectively. The mechanism of opioid antagonist action on growth is not well understood. We established a tissue culture model of LDN and HDN using short-term and continuous opioid receptor blockade, respectively, in human ovarian cancer cells, and found that the duration of opioid receptor blockade determines cell proliferative response. **The alteration of growth by NTX also was detected in cells representative of pancreatic, colorectal and squamous cell carcinomas.** The opioid growth factor (OGF; [Met 5]-enkephalin) and its receptor (OGFr) were responsible for mediating the action of NTX on cell proliferation. NTX upregulated OGF and OGFr at the translational but not at the transcriptional level.The mechanism of inhibition by short-term NTX required p16 and/or p21 cyclin-dependent inhibitory kinases, but was not dependent on cell survival (necrosis, apoptosis). Sequential administration of short-term NTX and OGF had a greater inhibitory effect on cell proliferation than either agent alone. Given the parallels between short-term NTX in vitro and LDN in vivo, we now demonstrate at the molecular level that the OGF–OGFr axis is a common pathway that is essential for the regulation of cell proliferation by NTX.

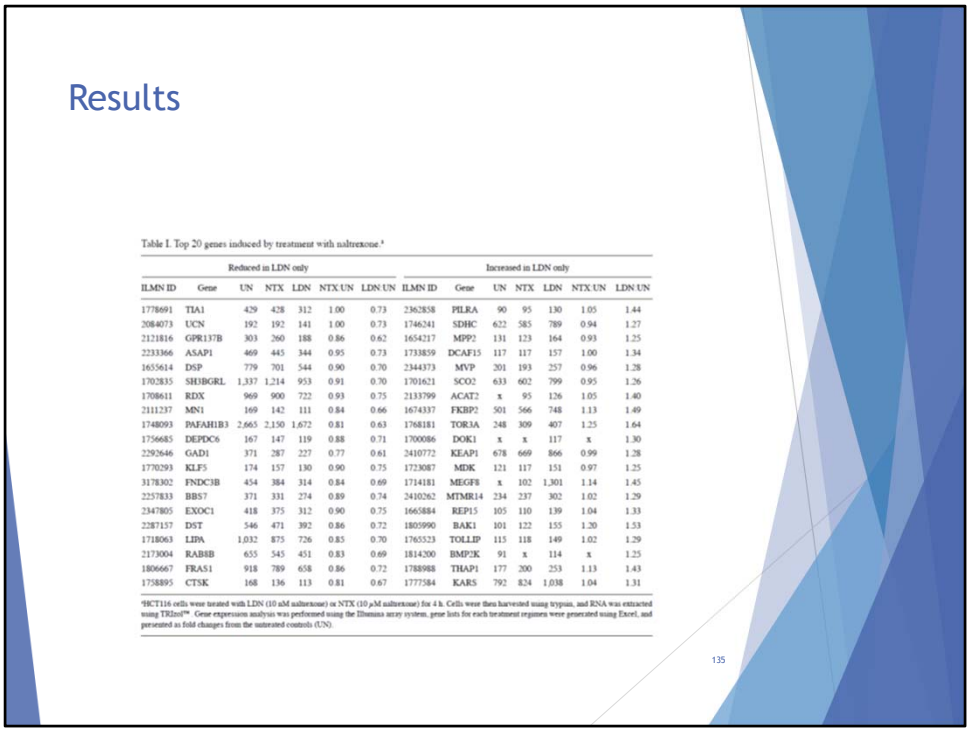
2. Growth inhibition of thyroid follicular cell-derived cancers by the opioid growth factor (OGF) - opioid growth factor receptor (OGFr) axisPatricia J McLaughlin1*, Ian S Zagon1, Sunny S Park2, Andrea Conway1, Renee N Donahue1 and David Goldenberg2 (http://www.biomedcentral.com/1471-2407/9/369)

Background: Carcinoma of the thyroid gland is an uncommon cancer, but the most frequent malignancy of the endocrine system. Most thyroid cancers are derived from the follicular cell. Follicular carcinoma (FTC) is considered more malignant than papillary thyroid carcinoma (PTC), and anaplastic thyroid cancer (ATC) is one of the most lethal human cancers. Opioid Growth Factor (OGF; chemical term - [Met 5]-enkephalin) and its receptor, OGFr, form an inhibitory axis regulating cell proliferation. Both the peptide and receptor have been detected in a wide variety of cancers, and OGF is currently used clinically as a biotherapy for some non-thyroid neoplasias. This study addressed the question of whether the OGF-OGFr axis is present and functional in human thyroid follicular cell - derived cancer.

Methods: Utilizing human ATC (KAT-18), PTC (KTC-1), and FTC (WRO 82-1) cell lines, immunohistochemistry was employed to ascertain the presence and location of OGF and OGFr. The growth characteristics in the presence of OGF or the opioid antagonist naltrexone (NTX), and the specificity of opioid peptides for proliferation of ATC, were established in KAT-18 cells. Dependence on peptide and receptor were investigated using neutralization studies with antibodies and siRNA experiments, respectively. The mechanism of peptide action on DNA synthesis and cell survival was ascertained. The ubiquity of the OGF-OGFr axis in thyroid follicular cell-derived cancer was assessed in KTC-1(PTC) and WRO 82-1 (FTC) tumor cells.

LDN and cancer therapy

- Liu et al studied the effects of LDN on human colorectal cancer and lung cancer cells
  - In vitro
- Used LDN concentrations of 1 and 10 nM
- Normal naltrexone (NTX) concentrations of 1 and 10 μM
- Used RNA extraction and microarray analysis
  - Determined the different effects of LDN and naltrexone on gene induction and protein expression (ex. BAD and BIK1)
- Pre-treated cells with LDN or NTX then added chemotherapeutic agents such as cyclophosphamide, gemcitabine, and oxaliplatin.



BAK1 (an apoptotic gene) was increased significantly after the treatment with LDN but not NTX

Paired immunoglobulin-like type 2 receptor alpha (PILRA) induced with LDN but not NTX. PILRA is involved in the regulation of the immune system

Results

Table II. Effect of NTX and LDN on cell cycle-related genes in HCT116 cells.[a]

		Raw data			Relative to UN		
Process	Gene	UN	NTX	LDN	NTX/UN	LDN/UN	LDN/NTX
DNA damage	p53	271	257	251	0.95	0.93	0.98
CDKi	p21	2,022	1,780	1,776	**0.88**	**0.88**	1.00
	p27	441	400	398	0.91	0.90	0.99
	p57	211	161	171	**0.77**	**0.81**	1.06
	p19	202	246	262	**1.22**	**1.30**	1.07
	p18	91	92	-	1.02	-	-
	p16	198	234	246	**1.18**	**1.24**	1.05
	p15	153	137	133	0.90	**0.87**	0.97
G0	cy C	669	729	696	1.09	1.04	0.95
	CDK3	93	98	91	1.06	0.98	0.93
G1 (early)	cy D1	6,580	6,773	6,574	1.03	1.00	0.97
	cy D2	95	96	91	1.01	0.96	0.95
	cy D3	1,247	1,542	1,511	**1.24**	**1.21**	0.98
	CDK4	3,528	3,541	4,345	1.00	**1.23**	**1.23**
	CDK6	550	682	768	**1.24**	**1.40**	**1.13**
G1 (mid)	cy E1	357	453	455	**1.27**	**1.27**	1.00
	cy E2	491	804	766	**1.64**	**1.56**	0.95
	CDK2	765	974	989	**1.27**	**1.29**	1.02
S	cy A2	1,473	1,933	2,040	**1.31**	**1.38**	1.06
	CDK2	765	974	989	**1.27**	**1.29**	1.02
M	cy B1	1,328	1,715	1,919	**1.12**	**1.26**	**1.12**
	cy B2	2,530	2,686	2,806	1.06	**1.11**	1.04
	cy B3	105	97	96	0.93	0.92	0.99
	CDK1	1,016	1,378	1,207	**1.36**	**1.19**	**0.88**

[a]Cells were treated with LDN (10 nM naltrexone) or NTX (10 μM naltrexone) for 4 h. Cells were then harvested using trypsin, and RNA was extracted using TRIzol. Gene expression analysis was performed using the Illumina array system, and only genes related to cell cycle control and called present in at least one treatment included in the lists. Genes were categorized based upon cell cycle phase, and those altered by >10% in either direction are in bold.

136

Genes involved in cell cycle and the effects LDN and NTX have on them
CDK1, 4, 6, and cyclin B1 were affected differently when treated with LDN or NTX

RESULTS

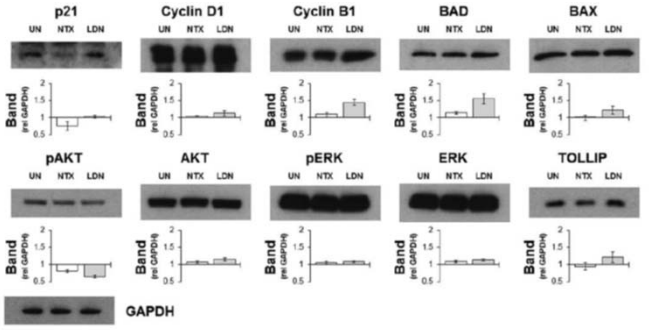


Figure 2. Effect of NTX and LDN on a collection of proteins in HCT116 cells. Cells were treated with LDN (10 nM naltrexone) or NTX (10 μM naltrexone) for 24 h. Cells were then harvested by scraping and lysed in RIPA buffer for western blot analysis. Selection of the proteins was guided in part by the gene expression data. Blots are representative of three separate experiments, and the densitometry represents the mean and SDs of these expressed relative to the respective GAPDH loading control.

137

Effects of NTX and LDN on proteins.
Cyclin B1, BAD, BAX increased when LDN administered
This figure shows that the induced or increased gene transcription led to an increase in the corresponding cell cycle protein.

results

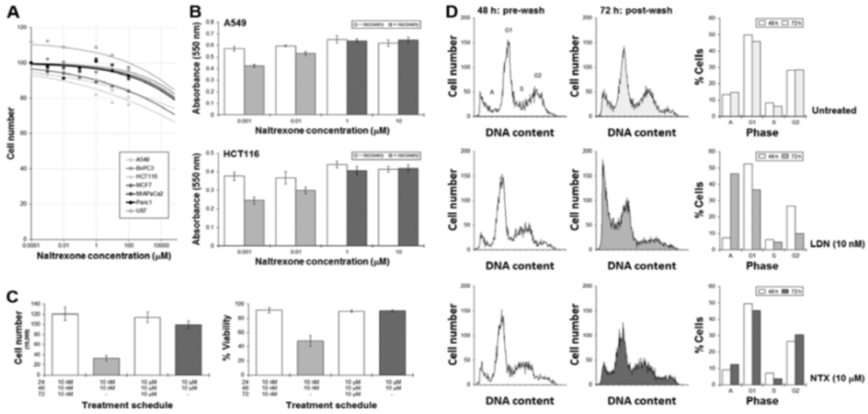


Figure 3. Effect of a drug-free period following culture with LDN or NTX. First the effect of a 72-h exposure to naltrexone was tested on a panel of cell lines and shown to be ineffectual at reducing cell numbers (A). A549 and HCT116 cells were then cultured with naltrexone at 1 nM, 10 nM, 1 μM and 10 μM. The first two concentrations were designated as LDN whilst the last two were conventional concentrations (NTX). After 48 h, media were aspirated and cells washed and re-cultured drug-free medium for a further 24 h. Parallel cultures were set up where cells were returned to drug-containing medium. MTT analysis (B) and cell counting using trypan-dye exclusion were performed on the cells (C - HCT116 alone). FACS analysis at 48 and 72 h were also done on HCT116 cells in an attempt to establish cell cycle distribution (D).

138

A- 72 hour exposure of LDN or NTX did not effectively reduce cell number
B,C- A549 and HCT16 cells treated with LDN and NTX for 48hrs, with lower doses of naltrexone the cells did not recover after the 24 hour drug free period. Thus, the cell number and % viability was decreased compared to the normal naltrexone doses.
D- shows cell number pre and post wash as well as the distribution of cells in the different phases of the cell cycle.

Results

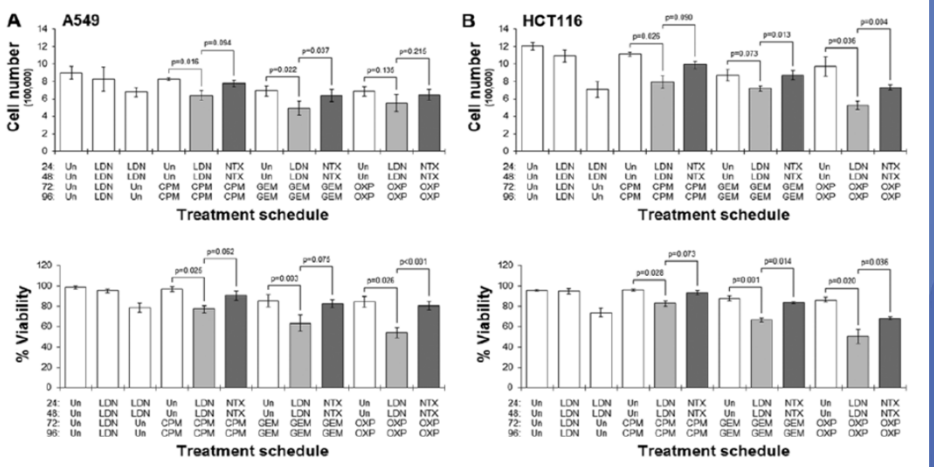


Figure 4. Effect of priming with LDN or NTX on A549 and HCT116 cells. Cells were cultured with 10 nM naltrexone (LDN) or 10 μM naltrexone (NTX) for 48 h before replacing the exhausted media with fresh media supplemented with cyclophosphamide (CPM, 100 μM for both cell lines), gemcitabine (GEM: 0.5 μM for both cell lines) or oxaliplatin (OXP, 1 μM for both). Cells were allowed to grow for another 48 h before assessing cell number and viability. Columns represent the means and SDs of three separate experiments. P-values are from paired Student's t-tests following analysis of variance to determine differences within the groups.

Pre-treatment with LDN or NTX followed by treatment with cyclophosphamide, gemcitabine, oxilaplatin

Pre-treatment with LDN led to increased

LDN before treatment with oxaliplatin significantly increased cell killing to 49±7.0 vs. 14±2.4% in cultures where priming was not used. cell death when treated with chemotherapeutic agents

Interestingly, priming with NTX before oxaliplatin resulted in just 32±1.8% cell killing.

Trends for cyclophosphamide and gemcitabine, LDN looks like it has a reduction in cell number and %viability

Summary

- LDN and NTX have different effects on cell cycle genes as well as genes that are commonly mutated in cancer cells
  - LDN increased gene expression of the apoptotic gene BAK1
- Pre-treatment with LDN led to an increase in cell death when followed by treatment with a cytotoxic chemotherapeutic agent
- This suggests that LDN is a potential partner in chemotherapeutic drug regimens
- This has only been tested in culture
  - Need human studies to determine the clinical significance

140

Low-Dose Naltrexone Studies

2014 Studies

The Use of LDN as a Novel Anti-Inflammatory Treatment for Chronic Pain

- Review of evidence that LDN may operate as a novel anti-inflammatory agent in the central nervous system, via action of microglial cells
- Currently used in fibromyalgia, Crohn's disease, multiple sclerosis, and complex regional pain syndrome
- Effects may be unique to LDN and appears to be independent from naltrexone's better known activity on opioid receptors
- LDN is well tolerated
- Current literature has small sample sizes, and few replications have been performed to help promote data
- LDN may represent one of the first glial cell modulators to be used for the management of chronic pain disorders

Varenicline, low dose naltrexone, and their combination for heavy-drinking smokers

- Heavy-drinking smokers (≥ 10 cigarrets/day) constitute a sizeable and hard-to-treat subgroup of smokers for whom tailored smoking cessation therapies are not yet available
- Double-blind randomized 2 x 2 medication design, testing varenicline alone (1 mg BID), LDN alone (25 mg QD), combination, and placebo
- 130 participants tested after a 9 day titration period designed to reach steady state on the target medication

Varencline, low dose naltrexone, and their combination for heavy-drinking smokers

- Testing completed at 12h of nicotine abstinence, after consuming a standard dose of alcohol and after smoking the first cigarette of the day
- Combination of Varencline and LDN was superior to placebo and monotherapy in:
  - Attenuating cigarette craving
  - Cigarette and alcohol “high”
  - Reduction of both cigarettes and alcohol during the 9 day medication titration period

2015 Studies

Initial Findings of an Open-Label Trial of Low-Dose Naltrexone for Symptomatic Mesenteric Panniculitis

- Lack of prospective studies and appropriate treatments for mesenteric panniculitis
- 4.5 mg for 12 weeks administered to 3 patients
- Primary endpoint: reduction in Mesenteric Panniculitis Subjective Assessment Score
- ESR and c-reactive protein tested at baseline
- All 3 patients had decrease in MPSAS at 4 weeks
  - 2 of 3 had decrease at 8 weeks
- Conclusion: LDN was safe, had minimal side effects , and showed efficacy in patients with symptomatic mesenteric panniculitis
- Further studies need to be conducted

Low Dose Naltrexone for Treatment of Multiple Sclerosis

- Retrospective chart review of safety and tolerability
- Multiple sclerosis is autoimmune disease of central nervous system
- Chart review of 215 patients with MS given oral LDN
- Study showed significant number of combination therapy of immunomodulating agent and LDN
- LDN did not cause any unexpected side effects and did not potentiate side effects of immunomodulating therapies

Low Dose Naltrexone Treatment of Established Relapsing-Remitting Experimental Autoimmune Encephalomyelitis

- Examined the modulation of opioid growth factor with low doses of naltrexone as disease modifying therapy for relapse-remitting autoimmune encephalomyelitis
- LDN treatment reduced behavioral scores across the 40 day observation point
- LDN increase the length of remission as well as the duration of mild disease
- Conducted in mice, so needs to be demonstrated in humans as well in further studies

2016 Studies

Combination of Levo-Tetrahydropalmatine and Low Dose Naltrexone: A Promising Treatment for Prevention of Cocaine Relapse

- Combination of L-THP and LDN targets both dopaminergic signaling and the regulation of endogenous opioids
  - Majority of pharmaceutics developed for treatment of substance abuse only target one pathway
- Evidence provided that this combination is more potent with fewer unwanted side effects than L-THP alone
- Conclusions
  - Combination has demonstrated significantly greater effect in attenuating drug seeking behavior than L-THP alone
  - Combination does not result in reduction of spontaneous locomotion
  - Combination increases peripheral concentrations of B-endorphin
  - L-THP and LDN appears to upregulate expression of POMC in the arcuate nucleus

Combination of Levo-Tetrahydropalmatine and Low Dose Naltrexone: A Promising Treatment for Prevention of Cocaine Relapse

- Pretreatment of L-THP and LDN significantly attenuated cocaine or cue-induced reinstatement of drug-seeking behavior
  - Dose-dependent manner
- Effective combination treatment for prevention of cocaine relapse
- L-THP and LDN mediates release of endogenous opioids and dopamine, allowing dopaminergic signaling in the brain to approach pre-addiction homeostasis
- Treats both behavioral and physiologic symptoms observed during recovery and reduces drug cravings and relapses
- Future studies should explore proposed mechanism of LDN as well as validate efficacy of L-THP and LDN in human trials

Off-Label, LDN for Refractory Painful Diabetic Neuropathy

- 2 mg dose of LDN showed to have partial improvement in burning pain of diabetic neuropathy
- 4 mg dose for 2 weeks produced even better pain relief
- Sleep improved after the treatment
- On examination, there was no hyperalgesia, but the sensory loss was not improved
- Initially, mild diarrhea, nausea, and somnolence occurred with treatment but subsided spontaneously after a few days
- Proposed mechanisms includes:
  - Opioid receptor blockage causing compensatory release of endogenous opioids
  - Antagonism of TLR-4 on microalga, which produces a variety of inflammatory factors such as pro-inflammatory cytokines, substance P, nitric oxide, and excitatory amino acids

2017 Studies

Low-Dose Naltrexone for the Treatment of Sarcoidosis

- Case report of a patient with Systemic sarcoidosis treated with LDN
- LDN increased endorphin levels and helped regulate inflammation including lymphocyte activity
- Radiographic improvement was seen
- Clinical improvement marked by less fatigue and no more need for antibiotic therapy for a sarcoid rash
- Unclear is the perceived improvement in dyspnea is directly responsible from the LDN
- Fatigue is the most common problem in sarcoidosis and can be secondary to pulmonary hypertension, chronic inflammation, infections, and drug side effects
  - LDN may have improved fatigue by reducing inflammation burden

Low-Dose Naltrexone Treatment of Familial Benign Pemphigus

- 3 patients with biopsy-proven recalcitrant Hailey-Hailey Disease were treated with LDN 1.5 mg to 3 mg
- Clinical response included healing of erosions, improvement of erythema, and alleviation of pain
- 3 patients exhibited at least 80% improvement in extent of disease
  - One patient had 90% clearance
  - All 3 patients had substantial improvement in QOL
- No adverse effects recorded

Naltrexone Inhibits IL-6 and TNF-alpha

- Analyzed effects of LDN on IL-6 secretion by peripheral blood mononuclear cells
  - In vitro following stimulation with ligands for TLR4 and for intracellular receptors TLR7, TLR8, and TLR9
- Naltrexone did not affect cell viability or induce apoptosis of PBMC
- Intracellular staining showed that naltrexone inhibited production of IL-6 and TNF-alpha by monocyte and plasmacytoid dendritic cell subsets
  - Within PBMC population following treatment with ligands for TLR7/8 and TL9, respectively

Naltrexone Inhibits IL-6 and TNF-alpha

- Naltrexone inhibited IL-6 production in isolated monocytes and B cells after TLR7/8 and TLR9 stimulation
- Findings indicate that naltrexone has potential to modulate the secretion of inflammatory cytokines in response to intracellular TLR activity
  - May have potential for use as an immunomodulator

LDN for Breakthrough MDD on Antidepressants

- Dopaminergic mechanisms of LDN proposed as augmentation for depressive breakthrough on pro-dopaminergic antidepressant regimens
- 12 adults with recurrent DSM-IV MDD on dopaminergic antidepressant regimens
  - Stimulants
  - Dopamine agonists
  - Bupropion $\geq$ 300 mg/day
  - Aripiprazole $\leq$ 2.5 mg/day
  - Sertraline $\geq$ 150 mg/day
- Given LDN 1 mg BID or placebo for 3 weeks

LDN for Breakthrough MDD on Antidepressants

- All 12 subjects completed the trial
- Hamilton depression rating scale (HAM-D-17 scores decreased from 12.2 to 11.7 for LDN
- Concussion: LDN augmentations showed some benefit for MDD relapse on dopaminergic agents
- Larger studies needed to confirm data

Reduced Pro-Inflammatory Cytokines after Eight Weeks of LDN for Fibromyalgia

- Fibromyalgia is a complex, multi-symptom condition that predominately affects women
- 10 week single-blind crossover trial to test the immune effects of eight weeks of oral administration of LDN
- 8 women enrolled
  - Average symptom severity was 62 out of 100
  - Average symptom duration of 14 years

Reduced Pro-Inflammatory Cytokines after Eight Weeks of LDN for Fibromyalgia

- Found that LDN was associated with reduced plasma concentrations of interleukins
  - Including: IL-1beta, IL1Ra, IL-2, IL-4, IL-5, IL6, IL-10, IL-12p40, IL-15, IL-17A, IL-27, INF alpha, TGF-alpha
- 15% reduction of fibromyalgia-associated pain and 18% reduction in overall symptoms
- Conclusion: LDN treatment in fibromyalgia is associated with a reduction of several key pro-inflammatory cytokines and symptoms
- More research needs to be conducted

Treatment of Hailey-Hailey Disease with Low-Dose Naltrexone

- Hailey-Hailey disease is a severe genetic blistering disease of intertriginous skin locations that can lead to poor QOL and increased morbidities
- The objective of this study was to determine if LDN is an effective treatment for Hailey-Hailey Disease
- Study was a case series performed at an outpatient dermatology clinic to 3 patients with severe Hailey-Hailey Disease recalcitrant to at least 4 therapies
- LDN 3 mg nightly, titrated to 4.5 mg in 2 patients
- Reductions in the size of lesions as well as subjective improvement of symptoms was found

Treatment of Hailey-Hailey Disease with Low-Dose Naltrexone

- All 3 patients noted significant healing of erosions and plaques starting from the peripheral aspect within 1 to 2 weeks of treatment
- Clinical resolution of lesions within 2 months of treatment
- Discontinuation of LDN resulted in flaring of symptoms, which cleared 2 to 3 days when re-challenged with LDN
- Conclusion: LDN is a novel therapy for Hailey-Hailey disease
- Possible mechanism may involve LDN influencing opioid or TLR signaling to improve calcium mobilization and improve keratinocyte differentiation and wound healing
- Further studies need to be conducted with larger samples sizes and to clarify the mechanism

2018 Studies

LDN for Gulf War Illness (GWI)

- Gulf War Illness- 30% of gulf war veterans developed GWI with chronic fatigue, pain, and neuropsychological disabilities.
- Double Blind, placebo controlled crossover trial of naltrexone 4.5 mg/day.
  - 37 participants
  - CGIS, VAS, SF-36 Health Survey, and Connors Continuous performance test assessed treatment response
- CGIS- improvement in 38% of patients
- SF-36- respondents showed less disability with respect to emotional limitations
- VAS- improvement in vertigo, depression, and confusion
- Conclusion: LDN may be effective for some with GWI, and further studies should be conducted

LDN for induction of remission in Inflammatory bowel disease patients

- 30% of patients with IBD are refractory to current drugs and will relapse
- 47 patients were prescribed 4.5 mg of naltrexone and followed for 12 weeks
- LDN induced clinical improvement in 74.5%, and remission in 25.5% of patients
- Naltrexone improved wound healing and reduced ER stress induced by tunicamycin, lipopolysaccharides, and bacteria in epithelial barriers.
- Conclusion: Naltrexone directly improves epithelial barrier function by improving wound healing and reducing mucosal ER stress levels. LDN is effective and safe, and should be considered for the treatment of therapy refractory IBD patients.

LDN CONDITION LIST

- **Cardiac (heart) diseases**
  - Autoimmune cardiomyopathy
  - Dressler's syndrome
  - Kawasaki's disease
  - Polyarteritis nodosa
  - Pyoderma gangrenosum
  - Subacute bacterial endocarditis (SBE)
- **Chronic Pain**
  - Complex Regional Pain Syndrome/RSD
- **Dermatologic (skin) diseases**
  - Alopecia areata
  - Anti-synthetase syndrome
  - Atopic allergy
  - Atopic dermatitis
  - Autoimmune progesterone dermatitis
  - Autoimmune thrombocytopenic purpura
  - Autoimmune urticaria
  - Bechet's syndrome
  - Blau syndrome
  - Bullous pemphigoid
  - Cicatricial pemphigoid
  - Cutaneous leukocytoclastic angiitis
  - Degos disease (thrombotic vasculopathy)
  - Dercum's disease
  - Dermatitis herpetiformis
  - Dermatomyositis
  - Diffuse cutaneous systemic sclerosis
  - Discoid lupus erythematosus
  - Eczema

LDN CONDITION LIST

- Epidermolysis bullosa acquisita
- Erythema nodosum
- Essential mixed cryoglobulinemia
- Hailey - Hailey Disease
- Henoch-Schonlein purpura
- Herpes gestationis
- Kawasaki's disease
- Lichen planus
- Lichen sclerosus
- Linear IgA disease
- Majeed syndrome
- Microscopic polyangiitis
- Morphea Mucha-Habermann disease
- Parry Romberg syndrome
- Pemphigus vulgaris
- POEMS syndrome
- Psoriasis
- Pyoderma gangrenosum
- Schnitzler syndrome
- **Ears, Nose, Sinus, Throat**
  - Autoimmune inner ear disease
  - Churg-Strauss syndrome
  - Cogan syndrome
  - Ménière's disease
  - Susac's syndrome
- **Endocrine diseases**
  - Addison's disease
  - Autoimmune polyendocrine syndrome
  - Cushing's syndrome

LDN CONDITION LIST

- Diabetes mellitus type 1
- Graves' disease
- Hashimoto's thyroiditis
- Hypoglycemia
- Hypopituitary or Secondary adrenal insufficiency
- Hypothalamic Dysfunction
- Hypothyroidism
- Ord's thyroiditis
- POEMS syndrome
- Schmidt syndrome
- Thyroiditis

- **Gastrointestinal diseases**
  - Autoimmune hepatitis
  - Autoimmune enteropathy
  - Autoimmune pancreatitis
  - Celiac disease
  - Churg-Strauss syndrome
  - Crohn's disease
  - Eosinophilic gastroenteritis
  - Gastritis
  - Gastrointestinal pemphigoid
  - Lupoid hepatitis
  - Nonalcoholic steatohepatitis (NASH)
  - POEMS syndrome
  - Polyarteritis nodosa
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
  - Pyoderma gangrenosum
  - Schnitzler syndrome
  - Ulcerative colitis

LDN CONDITION LIST

- **Hematologic/blood marrow disorders**
  - Agammaglobulinemia
  - Antiphospholipid syndrome
  - Autoimmune aplastic anemia
  - Autoimmune hemolytic anemia
  - Autoimmune lymphoproliferative syndrome
  - Castleman's disease – lymph node hyperplasia
  - Cold agglutinin disease
  - Evan's syndrome
  - Majeed syndrome
  - Paroxysmal nocturnal hemoglobinuria (PNH)
  - Pernicious anaemia
  - Pure red cell aplasia
  - Pyoderma gangrenosum
- **Hepatology (Liver)**
  - Hepatitis C
- **Immunology**
  - Common Variable Immunodeficiency
  - Epstein Barr Virus
  - Pernicious Anemia
  - Vitiligo
- **Infectious diseases**
  - Complement component 2 deficiency – increase risk of infections
  - HIV
  - Hypogammaglobulinemia – leads to infections
  - Lyme Disease
  - PANDAS (Pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections)
  - Sydenham chorea

LDN CONDITION LIST

- **Malignancies/cancers**
  - Bladder Cancer
  - Breast Cancer
  - Carcinoid Colon & Rectal Cancer
  - Glioblastoma
  - Liver Cancer
  - Lung Cancer (Non-Small Cell)
  - Lymphocytic Leukemia (chronic)
  - Lymphoma (Hodgkin's and Non-Hodgkin's)
  - Malignant Melanoma
  - Multiple Myeloma
  - Neuroblastoma
  - Ovarian Cancer
  - Pancreatic Cancer
  - Prostate Cancer (untreated)
  - Renal Cell Carcinoma
  - Throat Cancer
  - Uterine Cancer
- **Neurologic diseases**
  - Acute disseminated encephalomyelitis
  - Acute hemorrhagic leukoencephalitis
  - Amyotrophic Lateral Sclerosis
  - Anti-mag IgM peripheral neuropathy
  - Autoimmune peripheral neuropathy
  - Bickerstaff's encephalitis
  - Charcot Marie Tooth syndrome
  - Chronic inflammatory demyelinating polyneuropathy
  - Cranial arteritis

LDN CONDITION LIST

- Guillain-Barré syndrome
- Hashimoto's encephalitis
- Idiopathic inflammatory demyelinating diseases
- Inflammatory demyelinating polyneuopathy
- Lambert-Eaton myasthenic syndrome
- Miller-Fisher syndrome
- Multiple Sclerosis
- Myalgic Encephalomyelitis
- Myasthenia gravis
- Neuromyelitis optica
- Neuromyotonia
- Opsoclonus myoclonus syndrome
- PANDAS (Pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections)
- Paraneoplastic cerebellar degeneration
- Parkinson's disease
- Parry Romberg syndrome
- Parsonage-Turner syndrome
- Perivenous encephalomyelitis
- POEMS syndrome
- Polyarteritis nodosa
- Progressive inflammatory neuropathy
- Rasmussen's encephalitis
- Restless leg syndrome
- Stiff person syndrome
- Susac's syndrome
- Sydenham chorea
- Tolosa-Hunt syndrome
- Transverse myelitis

LDN CONDITION LIST

- **Ocular (eye) diseases**
  - Autoimmune uveitis
  - Balo disease/Balo concentric sclerosis
  - Blau syndrome
  - Cogan syndrome
  - Kawasaki's disease
  - Miller-Fisher syndrome
  - Neuromyelitis optica
  - Ocular cicatricial pemphigoid
  - Opsoclonus myoclonus syndrome
  - Parry Romberg syndrome
  - Pars planitis
  - POEMS syndrome
  - Scleritis
  - Susac's syndrome
  - Sweet's syndrome
  - Sympathetic ophthalmia
  - Tolosa-Hunt syndrome
  - Vasculitis vitiligo
- **Psychological disorders**
  - Anxiety
  - Depersonalization/Derealization Disorder (but not DID)
  - General Anxiety Disorder (GAD)
  - Obsessive Compulsive Disorder (OCD)
  - Panic Disorder
  - Postpartum Depression
  - Premenstrual Dysphoric Disorder (PMDD)
  - Social Phobia
  - Trichotillomania

LDN CONDITION LIST

- Depression
- Dissociative Disorder
- Post-traumatic stress disorder
- **Pulmonary (lung) diseases**
  - Anti-synthetase syndrome
  - Asthma Churg-Strauss syndrome
  - Emphysema
  - Fibrosing alveolitis
  - Goodpasture's syndrome
  - Idiopathic pulmonary fibrosis
  - POEMS syndrome
  - Pyoderma gangrenosum
  - Sarcoidosis
- **Renal (kidney) and urologic diseases**
  - Anti-GBM/TBM Nephritis
  - Autoimmune Renal Neuropathy
  - Berger's disease - IgA nephropathy
  - Glomerulonephritis
  - Goodpasture's syndrome
  - IgA nephropathy
  - Interstitial cystitis
  - Microscopic polyangiitis
  - Paroxysmal nocturnal hemoglobinuria (PNH)
  - POEMS syndrome
- **Rheumatologic (arthritis and autoimmune) disorders**
  - Ankylosing spondylitis
  - Anti-synthetase syndrome
  - Chronic fatigue syndrome (CFS)

LDN CONDITION LIST

- Chronic recurrent multifocal osteomyelitis
- Complement component 2 deficiency – increase risk of lupus
- CREST syndrome
- Ehlers-Danlos Syndrome
- Enthesitis-related arthritis
- Eosinophilic fasciitis
- Fibrodysplasia ossificans progressiva
- Fibromyalgia
- Inclusion body myositis
- Juvenile idiopathic arthritis
- Juvenile rheumatoid arthritis – Still's disease
- Lupus erythematosus
- Majeed syndrome
- Mixed Connective Tissue Disease
- Morphea Myositis
- Palindromic rheumatism
- Polymyalgia rheumatica
- Polymyositis
- Psoriatic arthritis
- Raynaud phenomenon
- Reiter's syndrome
- Relapsing polychondritis
- Retroperitoneal fibrosis
- Rheumatoid arthritis
- Rheumatoid fever
- Sarcoidosis
- Schnitzler syndrome
- Scleroderma
- Sjögren's syndrome

LDN CONDITION LIST

- Spondylitis
- Spondyloarthropathy
- Undifferentiated connective tissue disease
- Undifferentiated spondyloarthropathy
- **Sleep Disorders**
  - Sleep Issues
- **Vasculitis**
  - Blau syndrome
  - Churg-Strauss syndrome
  - Essential mixed cryoglobulinemia
  - Giant cell arteritis
  - Kawasaki's disease
  - Leukocytoclastic vasculitis
  - Polyarteritis nodosa
  - Takayasu's arteritis
  - Temporal arteritis (also known as ""giant cell arteritis"")
- **Women's Health**
  - Infertility
  - polycystic ovary syndrome (PCOS)
- **Animals and LDN**

References

- Sushchyk S, Xi ZX, Wang JB. Combination of levo-tetrahydropalmatine and low dose naltrexone: A promising treatment for prevention of cocaine relapse. *J Pharmacol Exp Ther*. 2016;357:248-257.
- Initial findings of an open-label trial of low-dose naltrexone for symptomatic mesenteric panniculitis. *J Clin Gastroenterol*. 2015;49(9):794-5.
- Low dose naltrexone for treatment of multiple sclerosis: A retrospective chart review of safety and tolerability. *Journal of Clinical Psychopharmacology*. 2015;35(5):609-11.
- Hammer LA, Zagon IS, McLaughlin PJ. Low dose naltrexone treatment of established relapsing-remitting experimental autoimmune encephalomyelitis. *J Mult Scler*. 2015;2(2):1-9.
- Weinstock LB, Myers TL, Shetty A. Low-dose naltrexone for the treatment of sarcoidosis. *Sarcoidosis Vasculitis and Diffuse Lung Disease*. 2017;34;184-187.

References

- Ibrahim O, Hogan SR, Vij A, et al. Low-dose naltrexone treatment of familial benign pemphigus (Hailey-Hailey Disease). *JAMA Dermatology*. 2017;153(10):1015-17.
- Cant R, Dalgleish AG, Allen RL. Naltrexone inhibits IL-6 and TNF-alpha production in human immune cell subsets following stimulation with ligands for intracellular toll-like receptors. *Frontiers in Immunology*. 2017;8(809):1-8.
- Off-label, low-dose naltrexone for refractory painful diabetic neuropathy. *Pain Medicine*. 2016;17:790-791.
- Mischoulon D, Hylek L, Yeung AS. Randomised, proof-of-concept trial of low-dose naltrexone for patients with breakthrough symptoms of major depressive disorder on antidepressants. *Journal of Affective Disorders.* 2017;208:6-14.
- Parkitny L, Younger J. Reduce pro-inflammatory cytokines after eight weeks of low-dose naltrexone for fibromyalgia. *Biomedicines*. 2017;5(16):1-9.

References

- Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clin Rheumatol*. 2014;33:451-459.
- Albers LN, Arbiser JL, Feldman RJ. Treatment of Hailey-Hailey Disease with low-dose naltrexone. *JAMA Dermatology*. 2017;153(10):1018-20.
- Ray LA, Courtney KE, Ghahremani DG. Varencline, low dose naltrexone, and their combination for heavy drinking smokers: human laboratory findings. *Psychopharmacology*. 2014;231;3843-3853.

References (2018 Studies)

- Kori L. Brewer, Allison Mainhart & William J. Meggs (2018) Double-blinded placebo-controlled cross-over pilot trial of naltrexone to treat Gulf War Illness, Fatigue: Biomedicine, Health & Behavior, DOI: 10.1080/21641846.2018.1477034
- Lie, Mithcell R.K.L. et al. "LDN for Induction of Remission in Inflammatory Bowel Disease Patients." *BMC*, Journal of Transnational Medicine , 9 Mar. 2018, translational-medicine-biomedcentral-com.proxy.lib.umich.edu/articles/10.1186/s12967-018-1427-5.