Trial of Naltrexone & Dextromethorphan for Gulf War Illness

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Background

- Gulf War Illness
- Approximately 250,000 veterans of Gulf War
- No definitive treatment

Clinical Features of GWI

- Chronic Fatigue
- Chronic Pain
  - Headaches, diffuse muscle and joint pains
- Neuropsychological disabilities
  - Memory, cognition, concentration, sleep, libido, mood, irritability, inappropriate anger
- Subgroups with respiratory, GI, rash

hypothesis

- inflammatory cycle involving the brain
- may be a common mechanism of many neurological conditions
- whether initiated by toxic exposures, infection, or trauma

Pre-clinical Studies

- novel anti-inflammatory drugs may be of benefit in symptom-defined illnesses related to neuro-inflammation
- Dr. J. S. Hong's work at the NIEHS
- Morphine-related analogs, including naltrexone & dextromethorphan
- anti-inflammation and neuro-protective effects

Naltrexone HCl

- Generic drug
- FDA Approved Indications
  - Alcohol dependence
  - Opioid dependence
- Non-FDA Approved Indications
  - Drug withdrawal

Naltrexone HCl Adverse Effects

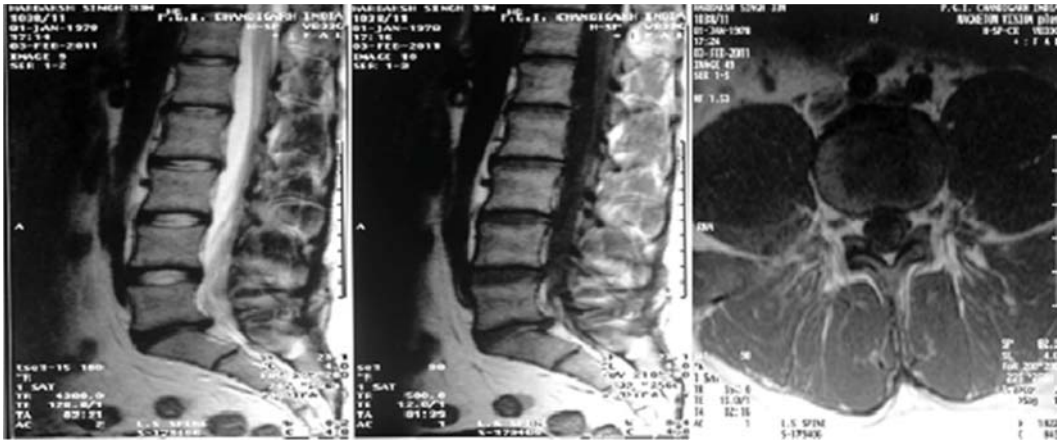
- asymptomatic elevations of hepatic transaminases (7% v 3% placebo)
- Clinically significant liver dysfunction has been reported in patients treated with naltrexone hydrochloride in clinical trials and during postmarketing surveillance
  - Often in association with alcoholic liver disease, viral hepatitis, use of other hepatoxic drugs

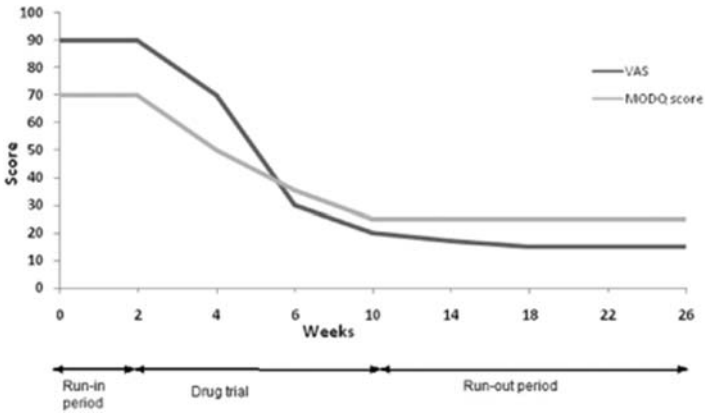
Naltrexone HCl Adverse effects

- Dizziness 13% v 4%
- Headache 21% v 18%
- Insomnia 13% v 12%
- Somnolence 5% v 1%

Low Dose Naltrexone: 4.5 mg/day

- Pilot trials of LDN
- Crohn's disease (Smith et al.)
- multiple sclerosis (Gironi et al.)
- cancer-related pain (Valentine et al.)
- Fibromyalgia (Younger et al.)
- Chronic low back pain (Ghai et al.)





Chronic low back pain
Case report
Ghai et al. 2014

Low dose naltrexone for fibromyalgia

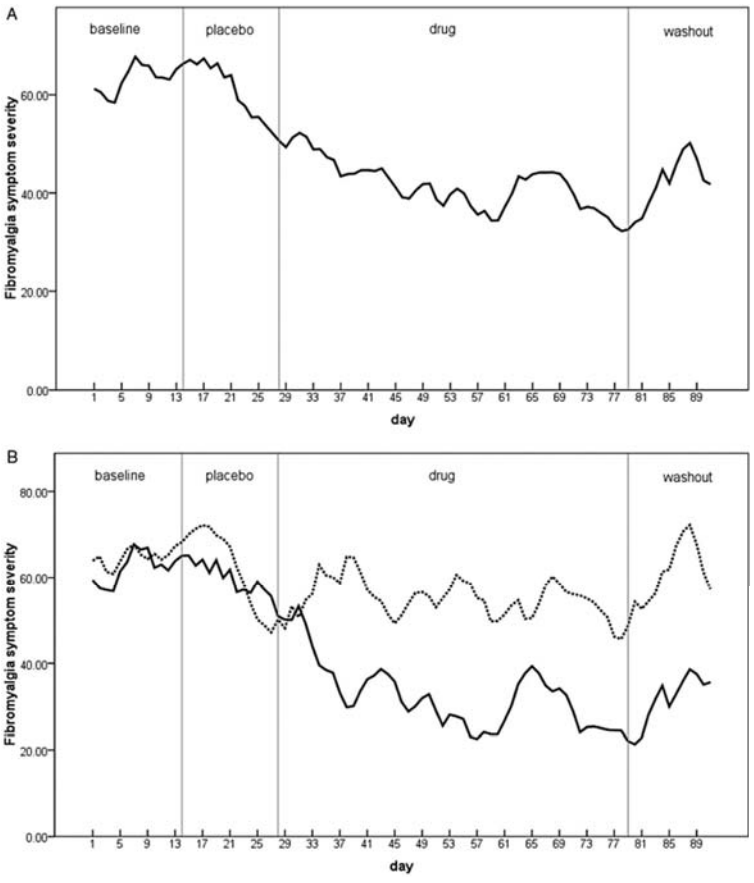


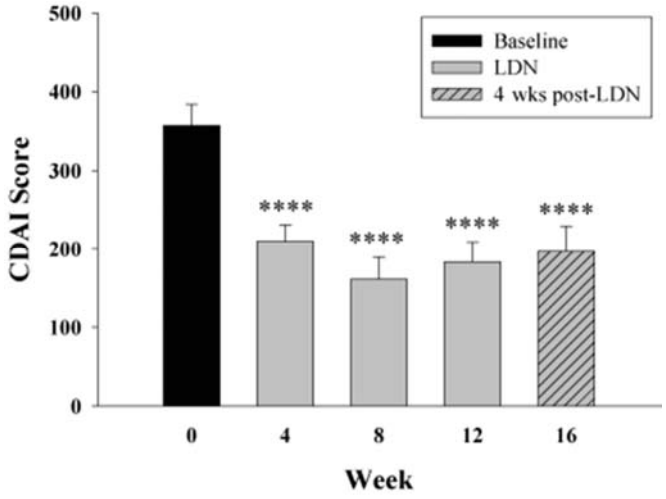
Figure 1. Overall, self-reported, daily fibromyalgia symptoms (scale 0–100, with 100 being most severe) as a function of placebo and low-dose naltrexone administration. Sections are: baseline, placebo, drug, and washout. A 3-day smoothing has been applied. (A) Data from all participants (N = 10). (B) Data separated by drug responders (30% or greater reduction of symptoms over placebo; solid line, N = 6) and nonresponders (broken line, N = 4).

Low Dose Naltrexone for Active Crohn's Disease

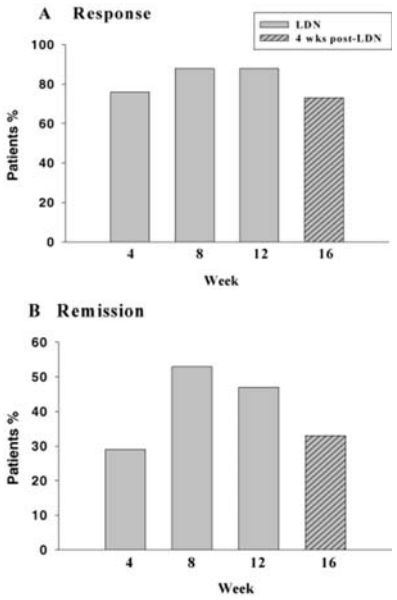
- open-labeled pilot prospective trial
- endoscopically confirmed active Crohn's disease (CDAI 220–450)
- 4.5 mg naltrexone/day for 12 weeks
- inflammatory bowel disease questionnaire (IBDQ) & short-form (SF-36) q 4 wk on therapy & 4 wk after completion

Active Crohn's Disease Results

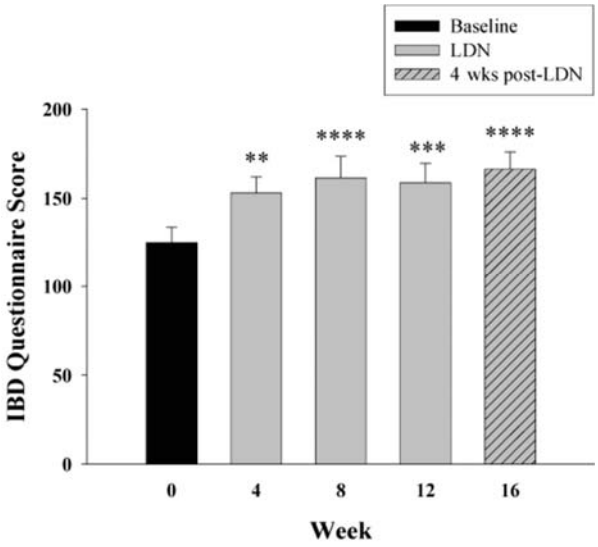
- 17 subjects
- mean CDAI score of 356
- CDAI scores decreased significantly ($P = 0.01$) with LDN
- remained lower than baseline 4 wk after completing therapy
- 89% response
- 67% remission ($P < 0.001$)
- Improvement in quality of life surveys
- sleep disturbances in 7 subjects



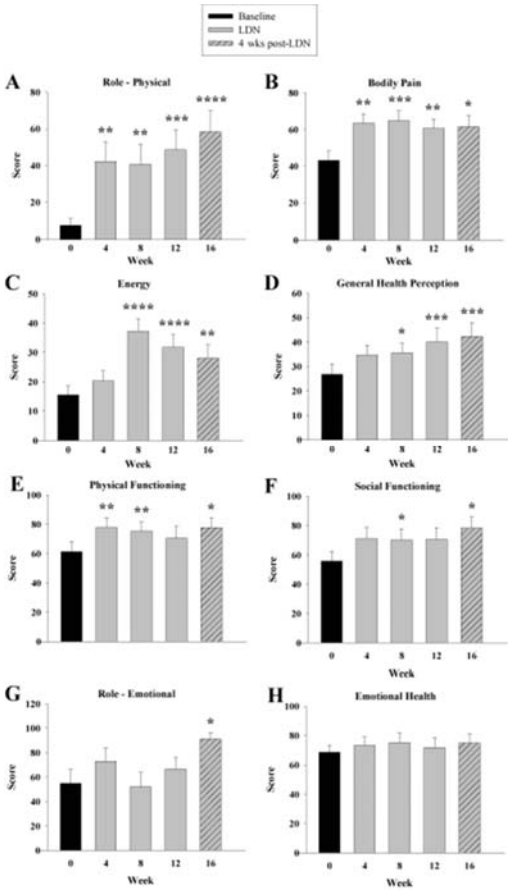
Mean Crohn's disease activity index (CDAI) scores SEM are shown at baseline (wk 0), wk 4, 8, and 12 after initiation of LDN therapy and 4 wk after discontinuation of LDN therapy (wk 16). ****Significantly different from baseline at $P < 0.0001$.



The percent of patients responding with a decline in CDAI score of at least 70 points (*A*), and the percent of patients achieving 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 therapy (wk 16).



Mean inflammatory bowel disease questionnaire (IBDQ) scores SEM are shown at baseline (wk 0), wk 4, 8, and 12 after initiation of LDN therapy, and 4 wk after discontinuation of treatment (wk 16). Significantly different from baseline at $^{**}P < 0.01$, $^{***}P < 0.001$, and $^{****}P < 0.0001$.



Mean SF-36 health survey scores SEM are shown at baseline (wk 0), wks 4, 8, 12 of LDN therapy, and 4 wk after discontinuation of treatment (wk 16) for each of the parameters measured by the SF-36 health survey. Significantly different from baseline values included the following: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

Conclusions
LDN for active Crohn's Disease

- LDN therapy appears effective and safe in subjects with active Crohn's disease.
- Further studies are needed to explore the use of this compound.

dextromethorphan

- Generic, available over the counter
- Cough suppressant similar to codeine
- Complex mechanisms of action
- Abused by overdose – similar to phencyclidine
- Hepatic metabolism
  - Variable by phenotype
  - Quinine may inhibit rapid metabolism

dextromethorphan

- animal studies
- Neuro-protective
  - anti-convulsion, anti-Parkinson's, protective in ischemia, anti-pseudobulbar (crying/laughing),
- Neurotoxic
  - neuropathologic mechanisms at high dose

Shin E-J et al. J Pharmacol Sci **116**, 137 – 148 (2011)

dextromethorphan

- Side effects
  - mild
  - drowsiness, fatigue, dystonia, & dizziness
- Serotonin syndrome
  - Primarily from drug interactions with anti-depressants
  - two case reports of serotonin syndrome associated with concurrent paroxetine and dextromethorphan therapy (Skop et al, 1994a; Skop et al, 1995).
  - Co-administration of dextromethorphan & monoamine oxidase inhibitors is contraindicated (deaths reported from serotonin syndrome, Rivers & Horner, 1970q; Sovner & Wolfe, 1988i)

dextromethorphan

- Toxicity
  - Seen at toxic but not therapeutic doses
  - euphoria, floating/flying sensation, hallucinations (auditory and visual), increased self-awareness, increased perception, increased sense of self, increased sociability, modification of sounds, and synesthesia (association of sounds with color)
  - inebriation

Methods

Materials

- naltrexone HCl 4.5 mg obtained by research pharmacist from compounding pharmacy
- dextromethrophan 60 mg BID (sustained release)
  - TSH Biopharm Corporation Ltd.
  - 3F-1, No. 3-1, Yuanqu St., Nangang Dist., Taipei, Taiwan (R.O.C.)

IRB Approval

- ECU IRB
  - Tough
  - 2 months
- DOD IRB
  - Tougher
  - 2 years
- CDMRP Statement of Work
  - Allow at least 6 months for IRB approval

Reasons for Delays in IRB Approval

- Slow turnaround
- IND Applications
- Modification of case definition
  - Co-morbidities developed over the 20 years that excluded many veterans using the initial Kansas case definition
- Modification of protocol
  - Exclusions due to drug interactions
  - Many veterans could take naltrexone or dextromethorphan but not both

FDA IND Applications

- Required by both IRBs for off label use of approved medications
- naltrexone
  - Requirement for IND waived by FDA
- dextromethorphan
  - No approved Sustained Release product on US market
  - IND required
  - analytical data on product required.

3 Arm Protocol: 11 months

Randomized, Double-Blinded trial

3 month course of Dextromethorphen, Naltrexone, or Placebo

One month wash out

3 month course of Dextromethorphen, Naltrexone, or Placebo

One month wash out

3 month course of Dextromethorphen, Naltrexone, or Placebo

Naltrexone Only Protocol: 7 Months

Veterans Taking Anti-depressants but no Opioids

Randomized, Double-Blinded trial

3 month course of Naltrexone or Placebo

One month wash out

3 month course of Naltrexone or Placebo

Dextromethorphan Only Protocol

Chronic opioid therapy but no antidepressants

Randomized, Double-Blinded trial

3 month course of Dextromethorphen or Placebo

One month wash out

3 month course of Dextromethorphen or Placebo

Recruitment (NC, SC, VA)

- Press releases
- Veterans groups
- VA clinics & hospitals
- Web site
- Postings
- Mailings

Screening Instrument

Patient: __ __ __ __ __ __ __ __ __ __ __ __

Patient Information Worksheet

Date of Initial Contact: __ __/ __ __ __/ __ __ __ __

Referring Method: _____

Screening Status:
- □ Denied-Inclusion/Exclusion Not Met/Met
- □ Follow Up
- □ Declined
- □ Approved

Consent Mailed: __ __ / __ __ __ / __ __ __ __

Script for Informed consent for telephone screening interview

You have been asked to participate in a screening phone call for a research study named: Trial of Naltrexone and Dextromethorphan for Gulf War Illness. This study is being conducted by William Joel Meggs, MD, in collaboration with Kori Brewer of the Brody School of Medicine at East Carolina University, Greenville, North Carolina, and is sponsored by the Department of Defense.

This clinical trial will examine the effects of Naltrexone and Dextromethorphan on people with Gulf War Illness. The trial will include visits to ECU for clinic appointments, laboratory procedures, history and physical examinations, medications, diary entries, and phone call appointments. Further testing will include various questionnaires and computer testing. The trial period is approximately 5-15 months from the date of consent.

I would like to ask you some questions that are of personal health information pertaining to your history before and after the Gulf War. These questions are to determine if you are eligible to participate in the study so please be as truthful and factual as possible with your answers. If you have questions as we go please ask so that you will have a complete understanding of the material.

Inclusion Criteria

1. Has served in the Gulf War ____yes ____no
2. Has developed a chronic multi-symptom illness ____yes ____no
3. Meets the Kansas Case definition of Gulf War Illness ____yes ____no
   (Complete Kansas Case Worksheet to Determine)

Exclusion Criteria-If the answer is "yes" patient is not eligible to be enrolled

1. Pregnant/Nursing Mothers ____yes ____no
2. Currently Taking (If yes please circle drug name)
   Taking the following medications, assigned to Dextromethorphan

- Alfentanil
- Alphaprodine
- Codeine
- Dihydrocodeine
- Ethylmorphine
- Fentanyl
- Hydrocodone
- Hydromorphone
- Levorphanol
- Meperidine

For each of the following symptoms, tell if you have it, how severe, and if it occurred before or after gulf war service. **YES Responses**

Veteran-reported symptoms that have persisted over the previous six months:

	None	Before war	After war		
Fatigue Domain			mild	moderate	severe
Fatigue	0	0	1	2	3
Feeling unwell after physical exercise or exertion	0	0	1	2	3
Problems getting to sleep or staying asleep	0	0	1	2	3
Not feeling rested after you sleep	0	0	1	2	3

Total Score, Fatigue Domain: _____

Pain Domain			mild	moderate	severe
Pain in your joints	0	0	1	2	3
Pain in your muscles	0	0	1	2	3
Body pain, where you hurt all over	0	0	1	2	3

Total Score, Pain Domain: _____

Neuro/cognitive/mood Domain	None	Before	mild	moderate	severe
Headaches	0	0	1	2	3
Feeling dizzy, lightheaded, or faint	0	0	1	2	3
Eyes very sensitive to light	0	0	1	2	3
Blurred or double vision	0	0	1	2	3
Numbness or tingling in your extremities	0	0	1	2	3
Tremors or shaking	0	0	1	2	3
Low tolerance for heat or cold	0	0	1	2	3
Night sweats	0	0	1	2	3
Having physical or mental symptoms after breathing in certain smells or chemicals	0	0	1	2	3
Difficulty concentrating	0	0	1	2	3
Difficulty remembering recent information	0	0	1	2	3
Trouble finding words when speaking	0	0	1	2	3
Feeling down or depressed	0	0	1	2	3
Feeling irritable or having angry outbursts					

Total Score, Neuro/cog/mood Domain: _____

Skin Domain	None	Before	mild	moderate	severe
Skin rashes	0	0	1	2	3
Other skin problems	0	0	1	2	3

Total Score, Skin Domain: _____

Gastrointestinal Domain	None	Before	mild	moderate	severe
Diarrhea	0	0	1	2	3
Nausea or upset stomach	0	0	1	2	3
Abdominal pain or cramping	0	0	1	2	3

Total Score, Gastrointestinal Domain: _____

Respiratory Domain	None	Before	mild	moderate	severe
Difficulty breathing or catching your breath	0	0	1	2	3
Frequent coughing when you don't have a cold	0	0	1	2	3
Wheezing in your chest	0	0	1	2	3

Total Score, Respiratory Domain: _____

Number of symptom domains having score of 2 or greater _____

<u>Summary of Kansas GWI case status criteria</u>:

1) No excluding diagnosed conditions, and

2) A total score of 2 or greater in at least 3 (of 6) symptom domains.

Clinical Evaluations

- History & Physical Examination
- Visual Analogue Scale
  - Symptoms scores
- SF-36
- Clinical Global Impression Scale
- Connor's Continuous Performance

Subject: _ _ _ _ _ _ _ _ _ _ _ _ _ _ Date: _ _/ _ _/ _ _ _ _
Visit: _ _

Visual Analogue Symptom Score Sheet

Instructions: place a mark on the line to indicate how severe the symptom is, with a mark on the left to indicate none and a mark on the right to indicate the most severe imaginable. These symptoms should be something you suffer from on a regular basis.q

Symptom: Headache

None _____ Extremely Severe

Symptom: Nasal Congestion

None _____ Extremely Severe

Symptom: Runny Nose

None _____ Extremely Severe

Symptom: Sinus Cavity Congestion or Pain

None _____ Extremely Severe

Symptom: Joint Aches

None _____ Extremely Severe

Symptom: Muscle Aches

None _____ Extremely Severe

Symptom: Nausea

None _____ Extremely Severe

Symptom: Vomiting

None _____ Extremely Severe

Symptom: Diarrhea

None _____ Extremely Severe

Symptom: Abdominal Pain

None _____ Extremely Severe

Symptom: Memory Problems

None _____ Extremely Severe

Symptom: Sleeping Problems

None _____ Extremely Severe

Symptom: Confusion

None _____ Extremely Severe

Symptom: Difficulty with Concentration

None _____ Extremely Severe

Symptom: Fatigue

None _____ Extremely Severe

Symptom: Rash

None _____ Extremely Severe

Symptom: Dizziness

None _____ Extremely Severe

Symptom: Vertigo

None _____ Extremely Severe

Symptom: Irritability

None _____ Extremely Severe

Symptom: Inappropriate Anger

None _____ Extremely Severe

Symptom: Depression

None _____ Extremely Severe

Symptom: Weight Loss

None _____ Extremely Severe

Symptom: Weight Gain

None _____ Extremely Severe

Symptom: Hallucinations

None _____ Extremely Severe

Symptom: loss of libido

None _____ Extremely Severe

Symptom: _____ (specify other)

None _____ Extremely Severe

Clinical Global Impression (CGI)

1. **Severity of illness**
   Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?
   0 = Not assessed
   1 = Normal, not at all ill
   2 = Borderline mentally ill
   3 = Mildly ill
   4 = Moderately ill
   5 = Markedly ill
   6 = Severely ill
   7 = Among the most extremely ill patients

2. **Global improvement:** Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.
   Compared to his condition at admission to the project, how much has he changed?
   0 = Not assessed
   1 = Very much improved
   2 = Much improved
   3 = Minimally improved
   4 = No change
   5 = Minimally worse
   6 = Much worse
   7 = Very much worse

3. **Efficacy index:** Rate this item on the basis of **drug effect only**.
   Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.
   EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		**Side effects**			
		None	*Do not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Outweighs therapeutic effect*
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

Laboratory Evaluations

- Routine
  - Complete blood count, comprehensive metabolic profile, UA
- Research
  - C-reactive protein (CRP)
  - Nerve growth factor
    - Eliza Assay,
    - EMD Millipore (http://www.emdmillipore.com/US/en). Billerica, Massachusetts.
  - Lincoplex human cytokine/chemokine panel
    - IL-1β, IL-6, IL-8, IL-10, IFN-γ, TNF-α,

Preliminary Results

Screening interview	301
Consent obtained	50
Completed naltrexone protocol	34
Completed dextromethorphan protocol	14
Withdrew	3
Loss to follow-up	8
Currently enrolled in naltrexone protocol	3
Currently enrolled in dextromethorphan protocol	11
Discontinued naltrexone due to adverse reaction (subjective dizziness)	1
Discontinued dextromethorphan due to adverse reaction	0

Demographics

- Mean age: 53.35 years (41-75)
- 38 men; 3 women
- 31 Caucasian; 7 African-American, 1 Hispanic
- Mean years in service 8.24 (1-36)

Branch of Service

Branch	Number of participants
Army	33
Marine Corp	14
Navy	3

Medication Use

- variety of psychotropic, seizure, analgesic, and anti-inflammatory medications used to treat symptoms of GWI
- Mean number of medications to treat symptoms was 1.9, and ranged from 0 to 11
- Visual analogue scores were not significantly different for those taking more than 2 medications relative to 2 or less except for greater fatigue and difficulty with sleep in those taking 2 or more medications

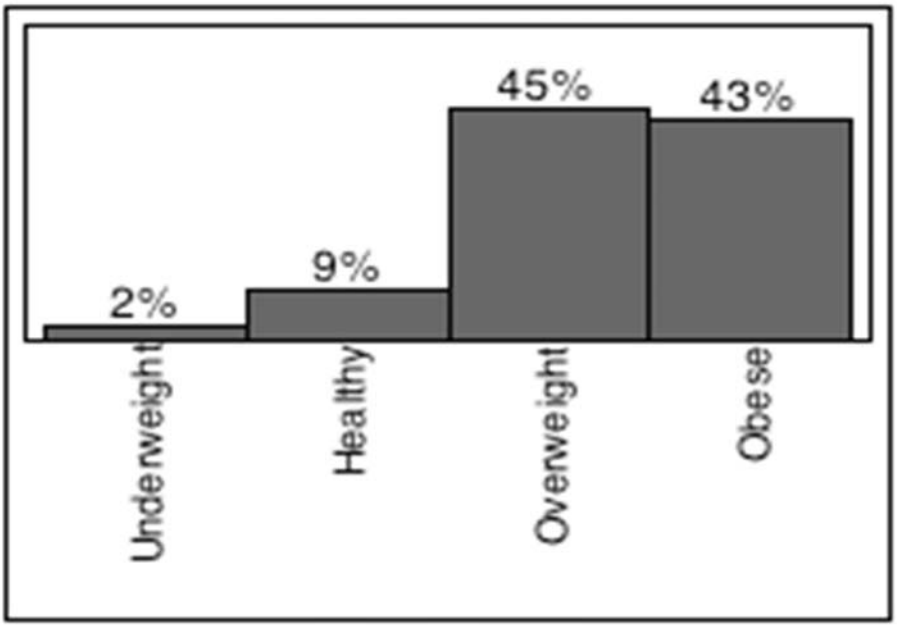
Medication Use

- Symptoms scores for fatigue were 86.2±36.6 cm (3+ medications) versus 58.2±33.8 cm (0, 1, or 2 medications) p=0.003
- scores for difficulty with sleep were 86.9±21.8 versus 66.7±29.7, p=0.02
- Those taking one or more medications relative to those taking no medications were more likely to report nasal congestion (p=0.02), sinus congestion/pain (p=0.001), and weight gain (p=0.04).

Physical Examinations

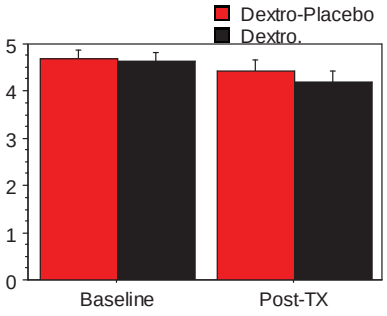
- Muscle & joint tenderness
- Over weight
- Abnormal upper respiratory examinations in 100%
  - Congestion, hypertrophic turbinates, injection, discoloration (blotchy pale to yellow)
- Decreased vibratory sense in 6%

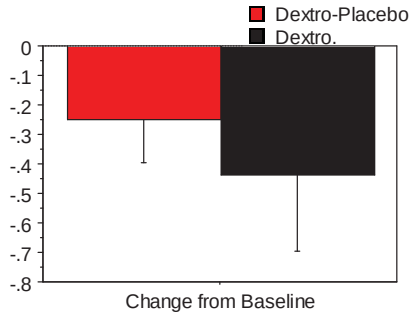
Body Mass Index



Highest BMI was 39

CGI Scores, Q#1, dextromethorphan





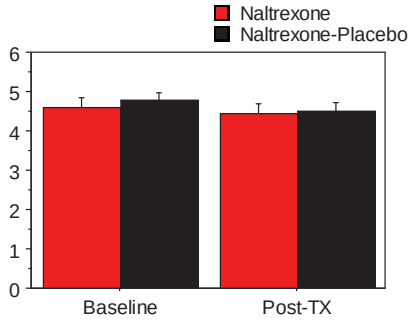
Unpaired Means Comparison for Change from Baseline
Grouping Variable: Treatment
Hypothesized Difference = 0

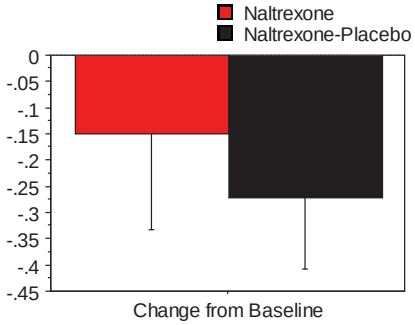
	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Dextro-Placebo, Dextro.	.188	30	.635	.5304	-.416	.791

Group Info for Change from Baseline
Grouping Variable: Treatment

	Count	Mean	Variance	Std. Dev.	Std. Err
Dextro-Placebo	16	-.250	.333	.577	.144
Dextro.	16	-.438	1.063	1.031	.258

CGI Q#1, naltrexone v placebo





Unpaired Means Comparison for Change from Baseline
Grouping Variable: Treatment
Hypothesized Difference = 0

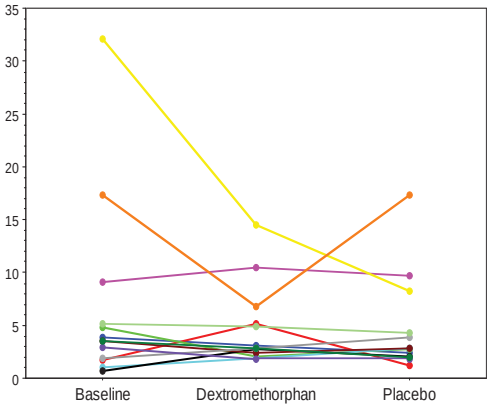
	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Naltrexone, Naltrexone-Placebo	.123	40	.549	.5858	-.329	.574

Group Info for Change from Baseline
Grouping Variable: Treatment

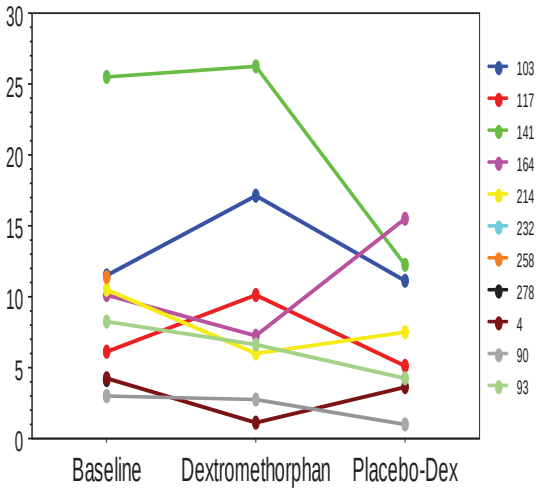
	Count	Mean	Variance	Std. Dev.	Std. Err
Naltrexone	20	-.150	.661	.813	.182
Naltrexone-Placebo	22	-.273	.398	.631	.135

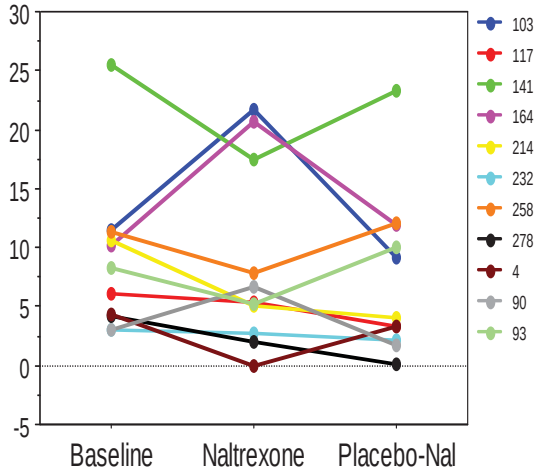
Laboratory Values

NGF, pg/mL

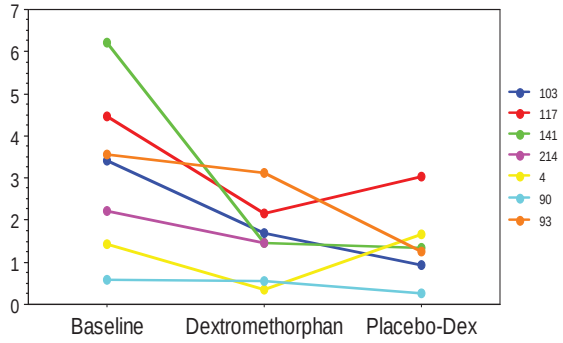


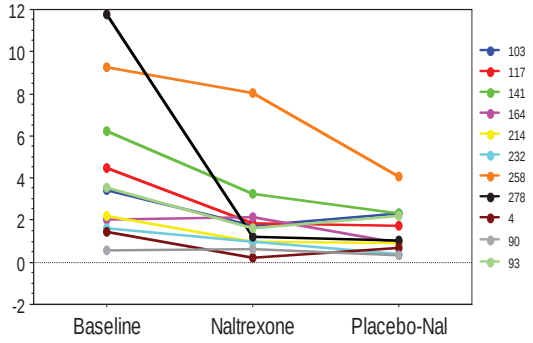
Interferon alpha
IFN: 13.1 ± 22.7 (0.14-126.8)



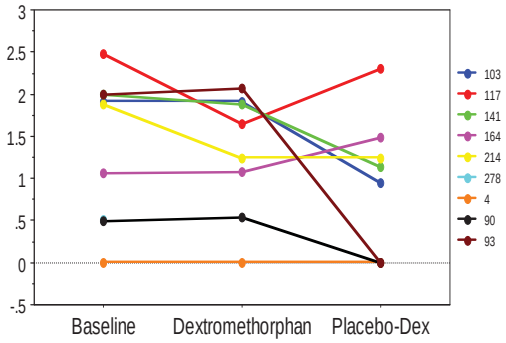


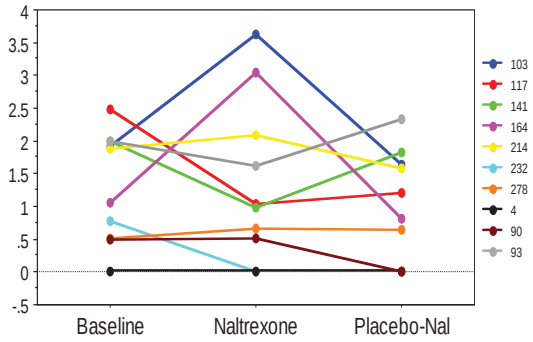
Interleukin 10



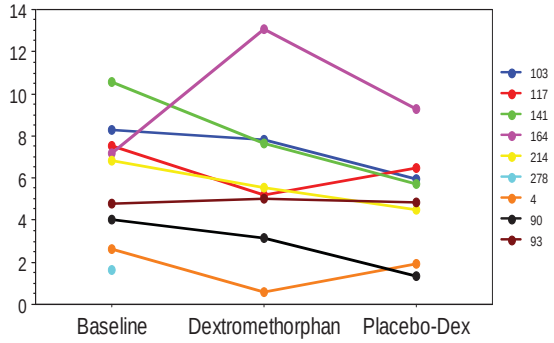


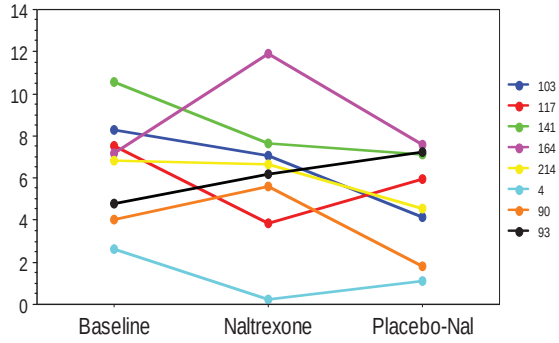
Interleukin 1 beta



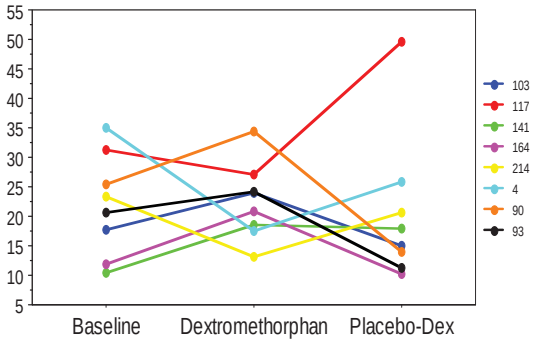


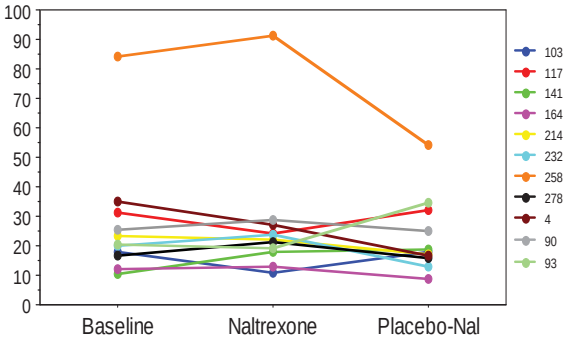
Interleukin 6



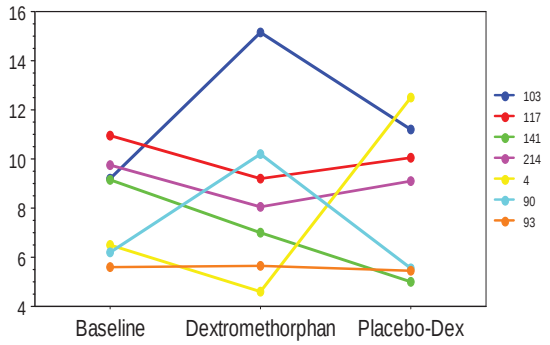


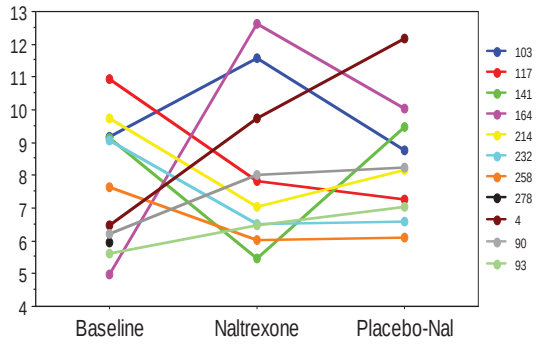
Interleukin 8



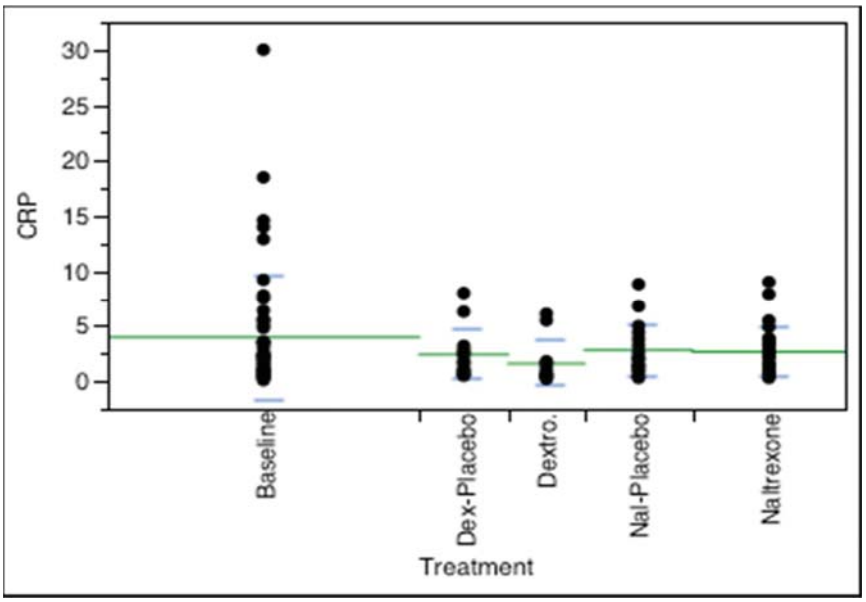


TNF-alpha





C-reactive protein

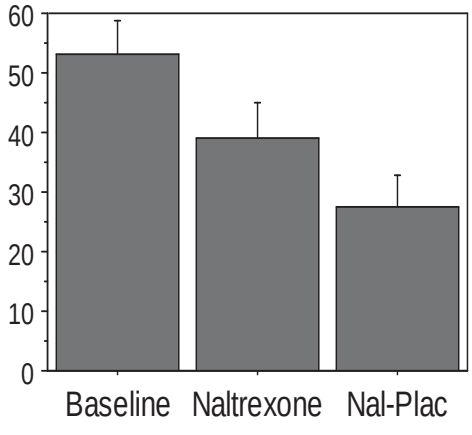


Mean CRP levels:
Baseline: 3.96
Dex: 1.59
Dex-Placebo: 2.4
Nal: 2.8
Nal-Placebo: 2.66

The difference between baseline and dex approaches significance p=0.07.
Power analysis shows that 26 people would be needed to reach 0.05 with 80% power (currently N = 13).

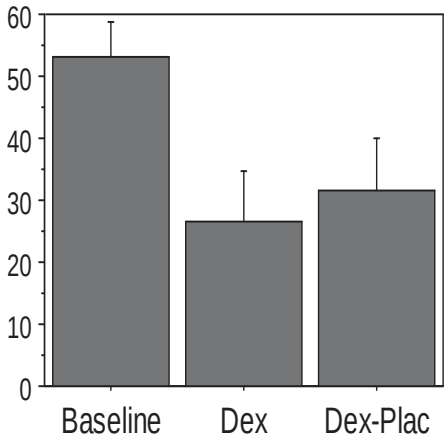
Symptom Scores

VAS scores for HA. Significantly decreased with both naltrexone, dex, and their respective placebos



Paired Means Comparison
Hypothesized Difference = 0

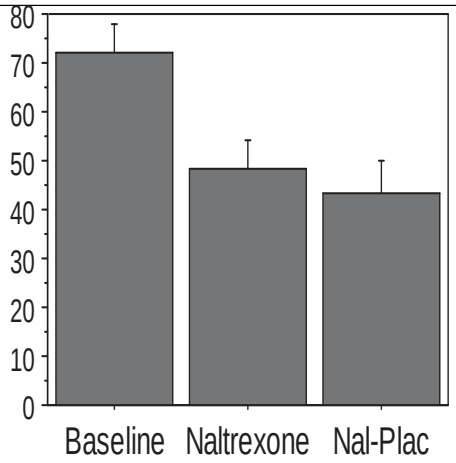
	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Naltrexone	15.893	27	3.159	.0039	5.571	26.215
Baseline, Nal-Plac	25.786	27	5.183	<.0001	15.577	35.994
Naltrexone, Nal-Plac	9.556	26	1.652	.1106	-2.337	21.448

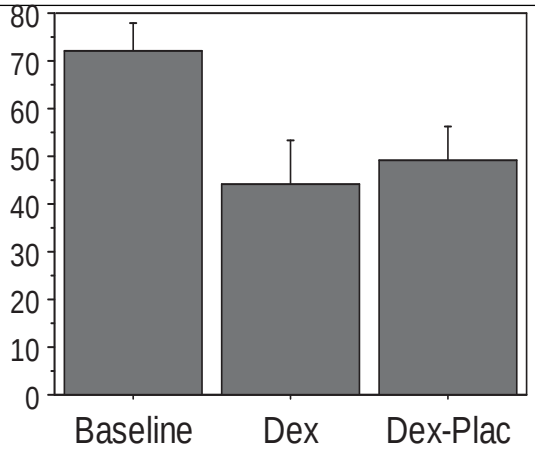


Paired Means Comparison
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Dex	27.200	14	4.707	.0003	14.806	39.594
Baseline, Dex-Plac	20.867	14	2.402	.0308	2.232	39.501
Dex, Dex-Plac	.357	13	.063	.9510	-11.949	12.663

VAS scores for sleeping problems. Significantly decreased with both naltrexone, dex, and their respective placebos





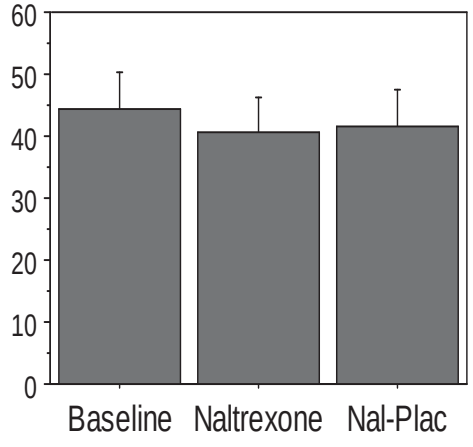
Paired Means Comparison
Hypothesized Difference = 0

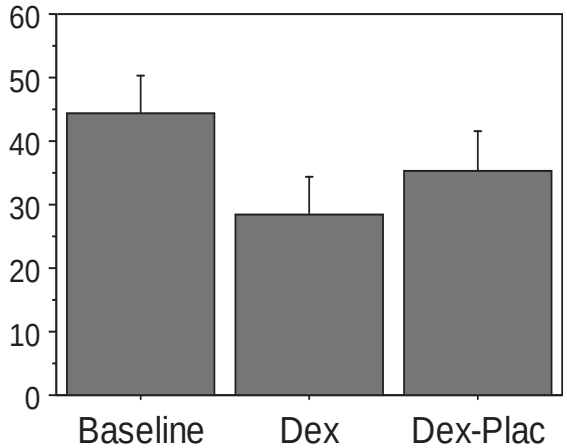
	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Naltrexone	25.741	26	4.730	<.0001	14.555	36.926
Baseline, Nal-Plac	30.444	26	4.771	<.0001	17.328	43.561
Naltrexone, Nal-Plac	2.385	25	.632	.5332	-5.387	10.157

Paired Means Comparison
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Dex	23.625	15	4.155	.0008	11.505	35.745
Baseline, Dex-Plac	16.563	15	2.345	.0332	1.510	31.615
Dex, Dex-Plac	-10.667	14	-1.509	.1534	-25.823	4.490

VAS scores for concentration problems. No effect of naltrexone or its placebo. Significantly decreased with dex, but not its placebo! POSITIVE FINDING!





Paired Means Comparison
Hypothesized Difference = 0

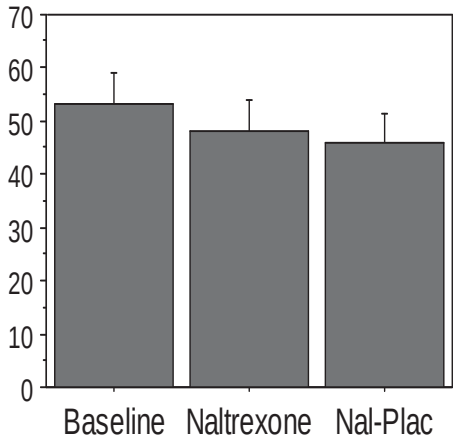
	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Naltrexone	7.296	26	1.749	.0921	-1.279	15.872
Baseline, Nal-Plac	6.556	26	1.131	.2684	-5.359	18.470
Naltrexone, Nal-Plac	-.962	25	-.193	.8488	-11.242	9.319

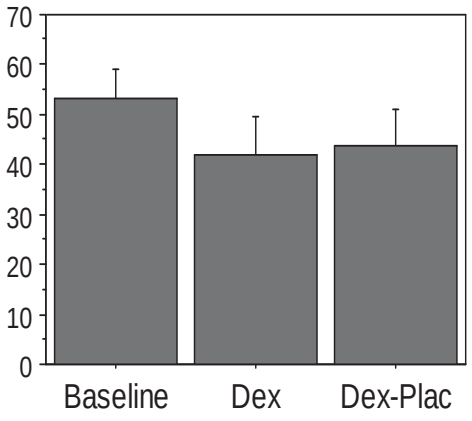
Paired Means Comparison
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Dex	18.313	15	2.766	.0144	4.201	32.424
Baseline, Dex-Plac	9.000	15	1.520	.1493	-3.622	21.622
Dex, Dex-Plac	-8.333	14	-2.271	.0394	-16.203	-.464

VAS scores for memory problems. Effect of naltrexone placebo and with Dex alone (but not its placebo).

POSITIVE FINDING!





Paired Means Comparison
Hypothesized Difference = 0

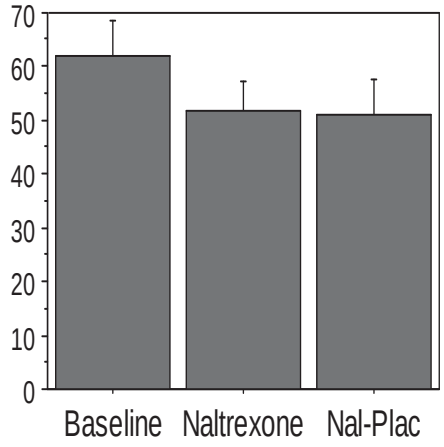
	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Naltrexone	9.370	26	1.856	.0749	-1.010	19.751
Baseline, Nal-Plac	11.852	26	2.565	.0164	2.355	21.349
Naltrexone, Nal-Plac	2.577	25	.583	.5649	-6.522	11.676

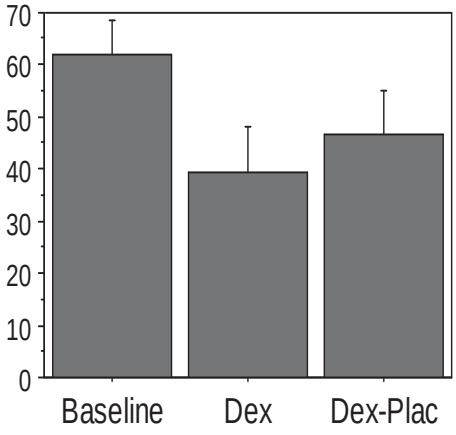
Paired Means Comparison
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Dex	13.750	15	2.102	.0528	-.190	27.690
Baseline, Dex-Plac	10.688	15	1.896	.0775	-1.330	22.705
Dex, Dex-Plac	-5.400	14	-1.253	.2307	-14.642	3.842

VAS scores for fatigue. Significant effect with naltrexone and its placebo. Also with Dex alone (but not its placebo).

POSITIVE FINDING!





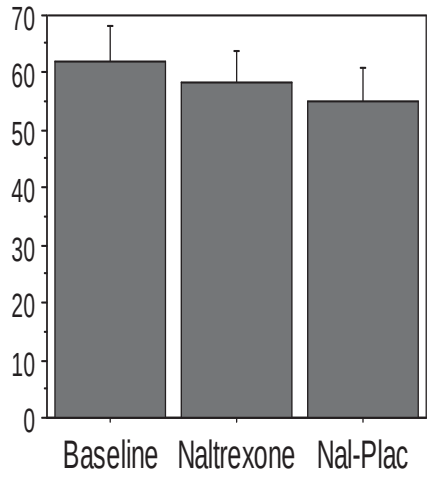
Paired Means Comparison
Hypothesized Difference = 0

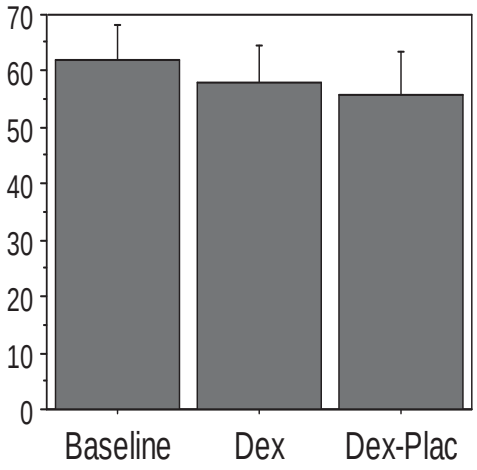
	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Naltrexone	13.407	26	2.378	.0251	1.817	24.998
Baseline, Nal-Plac	13.815	26	2.788	.0098	3.628	24.001
Naltrexone, Nal-Plac	.500	25	.082	.9353	-12.050	13.050

Paired Means Comparison
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Dex	20.625	15	2.875	.0116	5.333	35.917
Baseline, Dex-Plac	10.500	15	1.241	.2338	-7.539	28.539
Dex, Dex-Plac	-6.667	14	-.953	.3569	-21.674	8.341

VAS scores for joint pain. Nothing for either drug





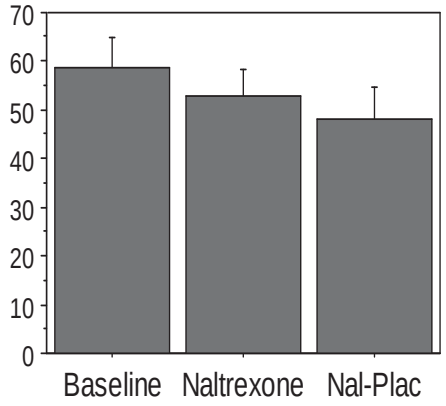
Paired Means Comparison
Hypothesized Difference = 0

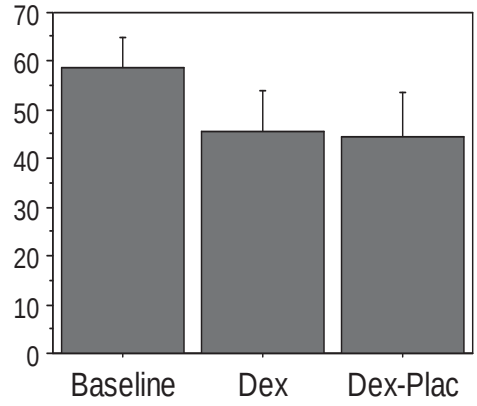
	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Naltrexone	2.148	26	.277	.7837	-13.773	18.070
Baseline, Nal-Plac	5.778	26	.699	.4907	-11.208	22.764
Naltrexone, Nal-Plac	1.923	25	.370	.7148	-8.794	12.641

Paired Means Comparison
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Dex	-.375	15	-.040	.9686	-20.342	19.592
Baseline, Dex-Plac	-1.063	15	-.101	.9210	-23.520	21.395
Dex, Dex-Plac	1.600	14	.215	.8329	-14.361	17.561

VAS scores for muscle aches. Nothing with naltrexone or its placebo. Effect with Dex alone (but not its placebo). POSITIVE FINDING!





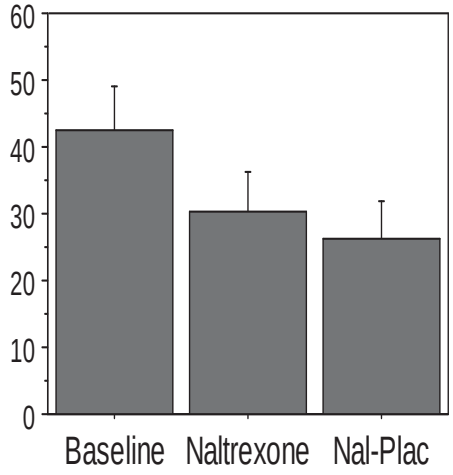
Paired Means Comparison
Hypothesized Difference = 0

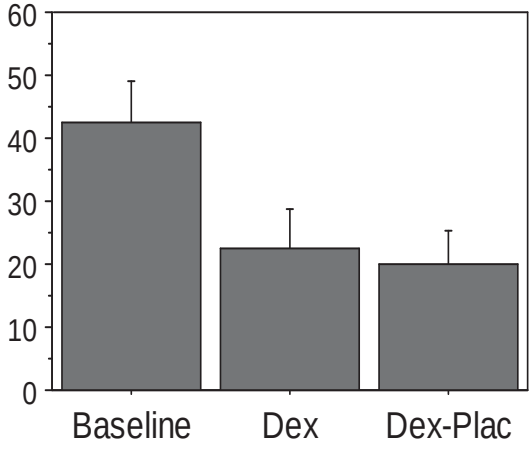
	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Naltrexone	6.630	26	1.148	.2615	-5.244	18.503
Baseline, Nal-Plac	10.481	26	1.749	.0921	-1.838	22.801
Naltrexone, Nal-Plac	5.654	25	1.051	.3032	-5.424	16.731

Paired Means Comparison
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Dex	11.938	15	2.332	.0340	1.028	22.847
Baseline, Dex-Plac	11.563	15	1.699	.1100	-2.946	26.071
Dex, Dex-Plac	1.000	14	.171	.8667	-11.550	13.550

VAS scores for inappropriate anger. Effect with naltrexone and its placebo. Nothing with Dex or its placebo





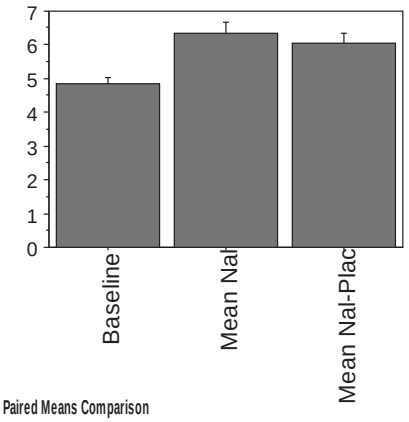
Paired Means Comparison
Hypothesized Difference = 0

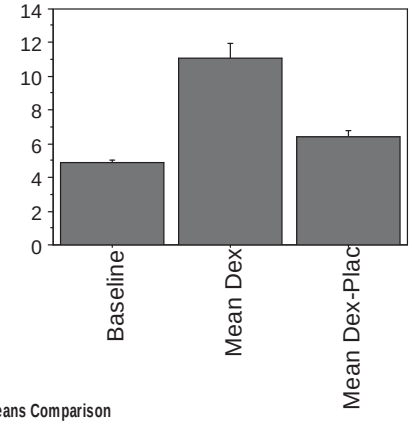
	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Naltrexone	14.889	26	2.326	.0281	1.730	28.048
Baseline, Nal-Plac	18.815	26	2.546	.0172	3.626	34.003
Naltrexone, Nal-Plac	4.154	25	.601	.5533	-10.081	18.389

Paired Means Comparison
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Dex	15.063	15	1.913	.0750	-1.719	31.844
Baseline, Dex-Plac	12.938	15	1.774	.0964	-2.610	28.485
Dex, Dex-Plac	-.400	14	-.099	.9226	-9.075	8.275

CGI scores significantly increased over baseline with naltrexone or its placebo. CGI scores significantly increased over baseline with Dex and its placebo..BUT Dex-placebo scores are significantly lower than Dex alone scores.





Paired Means Comparison
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Mean Nal	-1.432	26	-3.901	.0006	-2.187	-.677
Baseline, Mean Nal-Plac	-1.148	26	-3.217	.0035	-1.882	-.415
Mean Nal, Mean Nal-Plac	.333	25	.731	.4715	-.606	1.272

Paired Means Comparison
Hypothesized Difference = 0

	Mean Diff.	DF	t-Value	P-Value	95% Lower	95% Upper
Baseline, Mean Dex	-6.479	15	-7.450	<.0001	-8.333	-4.625
Baseline, Mean Dex-Plac	-1.833	15	-4.466	.0005	-2.708	-.958
Mean Dex, Mean Dex-Plac	4.844	14	4.526	.0005	2.549	7.140

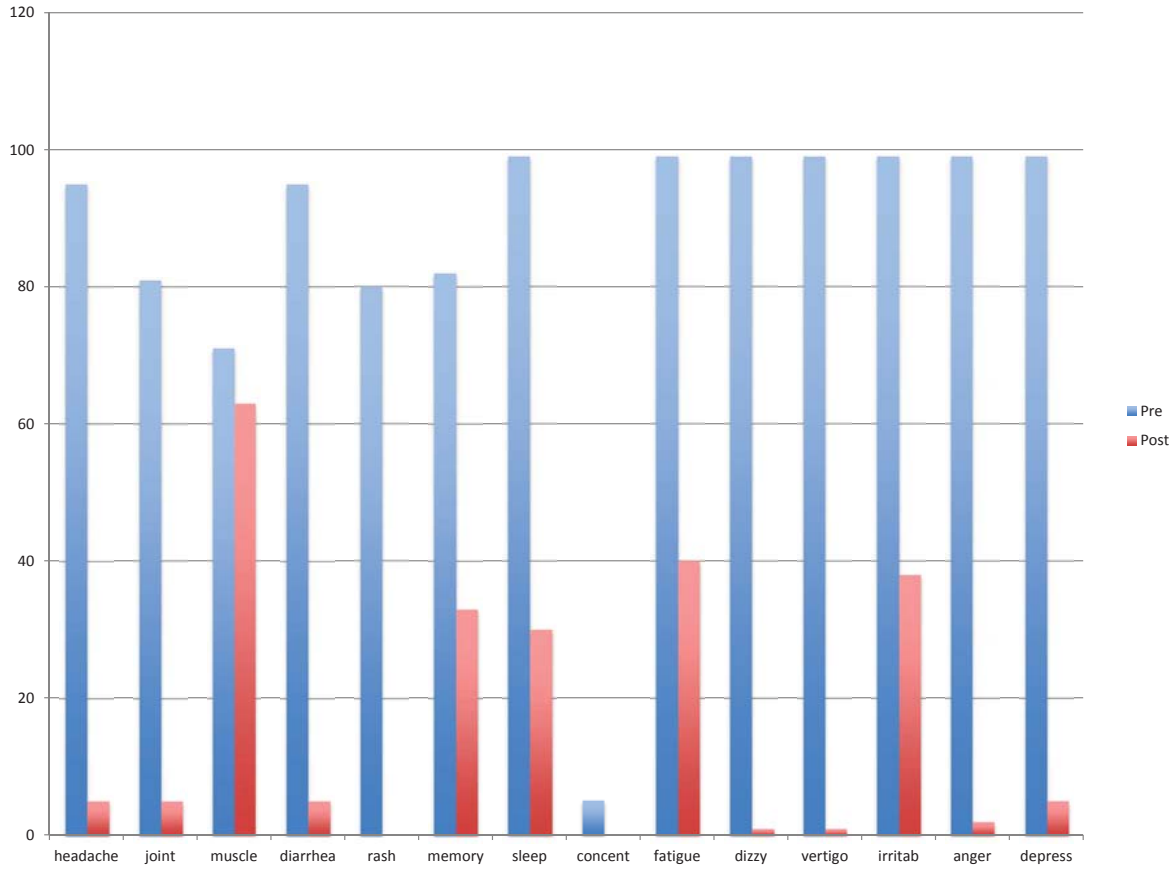
responder

Army infantry
GW age 21, in

	Naltrexone visit 1	Naltrexone visit 2
Headache	95	5
joint	81	5
muscle	71	63
diarrhea	95	5
rash	80	0
memory	82	33
Sleep	99	30
concentration	5	0
fatigue	99	40
dizziness	99	1
vertigo	99	1
irritability	99	38
anger	99	2
depression	99	5

Symptoms returned 2 days after stopped medication
Global clinical impression: severely ill to mildly ill
On celexa for depression, discontinued oxycodone and hydrocodone to participate
No rash at time of visit

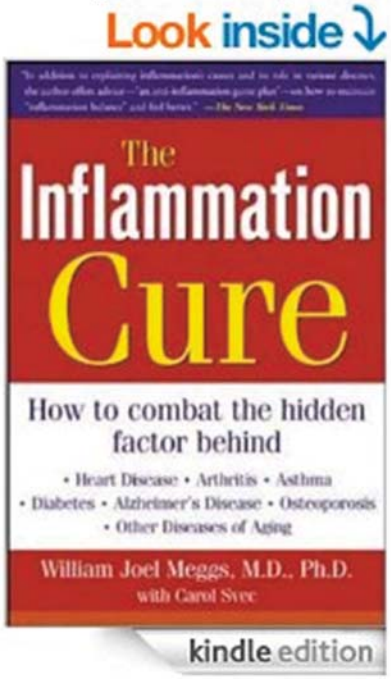
Exposures: 2 scud attacks, alarms went off, PB, oil well fires for one month, fumes from highway of death, vaccinations,

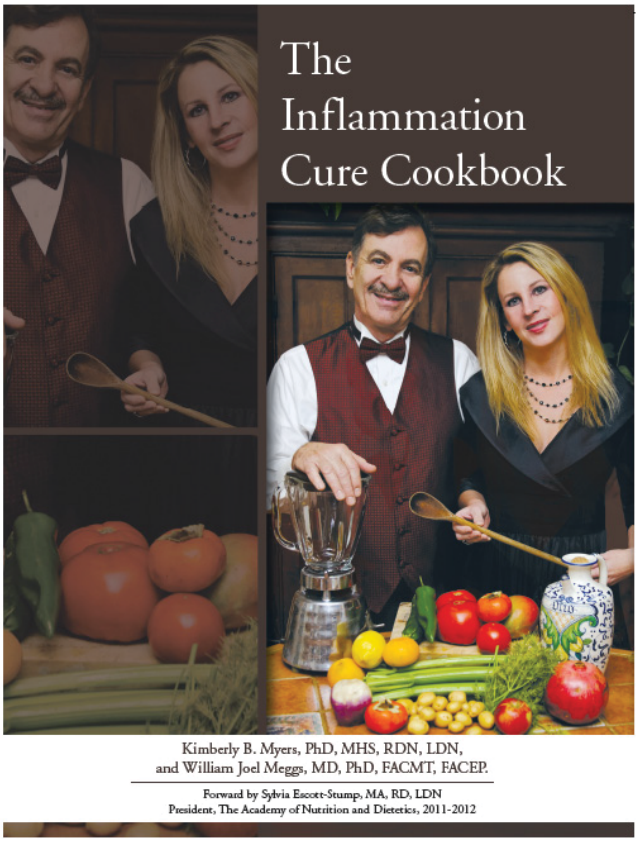


confounders

- Acute illnesses
  - Small bowel obstruction, pneumonia, acute sinusitis,
- Changes in therapy
  - Steroid injections, changes in psychotropic drugs, courses of antibiotics, corticosteroids
- Changes in diet and lifestyle

Confounded by Changes in Lifestyle





Part I
Food Choices

Part II
Recipes

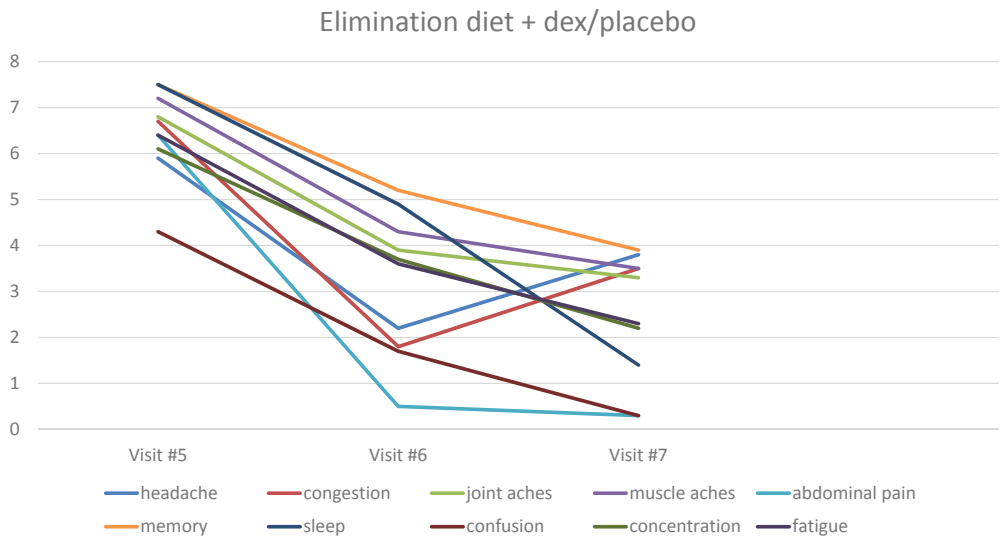
PART III
Identifying Personal Problem Foods

Part IV
Beyond what we eat – where we live & work, clean air, healthy lifestyles, good mind states, supplements, the chemical environment, what medicine can do

#237 confounder of dietary elimination eliminated sugar, caffeine, gluten, dairy lost 20 pounds in 10 days

symptom	**Visit #5**	**Visit #6**	**Visit #7**
Headache	5.9	2.2	3.8
Nasal congestion	6.7	1.8	3.5
Joint aches	6.8	3.9	3.3
Muscle aches	7.2	4.3	3.5
Abdominal pain	6.4	0.5	0.3
Memory problems	7.5	5.2	3.9
Sleeping problems	7.5	4.9	1.4
confusion	4.3	1.7	0.3
Concentration	6.1	3.7	2.2
fatigue	6.4	3.6	2.3

Response to dietary elimination +



Limitations

- No pharmacokinetic data
  - Genetic differences in metabolism
  - One dose for all, independent of weight & other factors
- No normal controls for NGF and Human cytokine/chemokine panels
- Snap shot limitation
- Concurrent treatments
  - "I got my knees injected."

Preliminary Conclusions

- At the doses used, there were responders & non-responders
- No statistical benefit when averaged over all participants
- NGF & cytokine panel data showed no consistent pattern of variability
- Empirical pharmacology treatments demonstrated no benefit relative to those using no medications

Lessons Learned
(or what would be done differently)

- Allow adequate times for IRB & FDA approvals
  - Don't use funds before approval
- Adjust doses using pharmacokinetic data
- Weekly VAS rather than pre- and post-symptoms scores
- Record VAS after discontinuation of medication

acknowledgements

- CDMRP for funding
- Dr. John Hong at NIEHS for proposing the study & advice
- Mr. Jim Binns for suggesting that I undertake the study
- Dr. Kori Brewer--scientist
- Allison Mainhart—clinical research specialist

References

- Skop BP, Finkelstein JA, Mareth TR, et al: The serotonin syndrome associated with paroxetine, an over-the-counter cold remedy, and vascular disease. Am J Emerg Med 1994c; 12:642-644.
- Rivers N & Horner B: Possible lethal reaction between Nardil and dextromethorphan (letter). Can Med Assoc J 1970k; 103:85.
- Smith JP, Stock H, Bigaman S, et al. Low-dose naltrexone therapy improves active Crohn's disease. *Am J Gastroenterol* 2007;**102**:820–828.

References

- Skop BP, Finkelstein JA, Mareth TR, et al: The serotonin syndrome associated with paroxetine, an over-the-counter cold remedy, and vascular disease. Am J Emerg Med 1994c; 12:642-644.
- Rivers N & Horner B: Possible lethal reaction between Nardil and dextromethorphan (letter). Can Med Assoc J 1970k; 103:85.
- Smith JP, Stock H, Bigaman S, et al. Low-dose naltrexone therapy improves active Crohn's disease. *Am J Gastroenterol* 2007;**102**:820–828.

References

- Ghai B et al. Off-Label, Low-Dose Naltrexone for Refractory Chronic Low Back Pain. Pain Medicine 2014;15:883-884.
- Gironi M, Martinelli-Boneschi F, Sacerdote P, et al. A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis. *Mult Scler* 2008;**14**:1076–1083.
- Valentine AD, Meyers CA, Talpaz M. Treatment of neurotoxic side effects of interferonalpha with naltrexone. *Cancer Invest* 1995;**13**:561–566