Trial of Naltrexone & Dextromethorphan for Gulf War Illness

William J. Meggs, MD, PhD
Brody School of Medicine
East Carolina University

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.)
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


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
2. Has developed a chronic multi-symptom illness
3. Meets the Kansas Case definition of Gulf War Illness

(Complete Kansas Case Worksheet to Determine)

Exclusion Criteria—if the answer is “yes” patient is not eligible to be enrolled

1. Pregnant/Nursing Mothers
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:

<table>
<thead>
<tr>
<th>Fatigue Domain</th>
<th>None</th>
<th>Before war</th>
<th>After war</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Feeling unwell after physical exercise or exertion</td>
<td>0</td>
<td>0</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Problems getting to sleep or staying asleep</td>
<td>0</td>
<td>0</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Not feeling rested after you sleep</td>
<td>0</td>
<td>0</td>
<td>1 2 3</td>
</tr>
</tbody>
</table>

Total Score, Fatigue Domain: ________

<table>
<thead>
<tr>
<th>Pain Domain</th>
<th>None</th>
<th>mild</th>
<th>moderate</th>
<th>severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain in your joints</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2 3</td>
</tr>
<tr>
<td>Pain in your muscles</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2 3</td>
</tr>
<tr>
<td>Body pain, where you hurt all over</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2 3</td>
</tr>
</tbody>
</table>

Total Score, Pain Domain: ________
### Neuro/cognitive/mood Domain

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

Total Score, Neuro/cog/mood Domain: ______

### Skin Domain

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Before</th>
<th>mild</th>
<th>moderate</th>
<th>severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rashes</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Other skin problems</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Total Score, Skin Domain: ______

### Gastrointestinal Domain

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Before</th>
<th>mild</th>
<th>moderate</th>
<th>severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nausea or upset stomach</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal pain or cramping</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Total Score, Gastrointestinal Domain: ______

### Respiratory Domain

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Before</th>
<th>mild</th>
<th>moderate</th>
<th>severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty breathing or catching your breath</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Frequent coughing when you don’t have a cold</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Wheezing in your chest</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Total Score, Respiratory Domain: ______

**Number of symptom domains having score of 2 or greater ______**

**Summary of Kansas GWI case status criteria:**
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

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.

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
<table>
<thead>
<tr>
<th>Symptom</th>
<th>None</th>
<th>Extremely Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint Aches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle Aches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory Problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeping Problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty with Concentration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom</td>
<td>Rating</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>Extremely Severe</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>Extremely Severe</td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>Extremely Severe</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>Extremely Severe</td>
<td></td>
</tr>
<tr>
<td>Inappropriate Anger</td>
<td>Extremely Severe</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Extremely Severe</td>
<td></td>
</tr>
<tr>
<td>Weight Loss</td>
<td>Extremely Severe</td>
<td></td>
</tr>
<tr>
<td>Weight Gain</td>
<td>Extremely Severe</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Extremely Severe</td>
<td></td>
</tr>
<tr>
<td>Loss of libido</td>
<td>Extremely Severe</td>
<td></td>
</tr>
<tr>
<td>Other Symptom (specify)</td>
<td>Extremely Severe</td>
<td></td>
</tr>
</tbody>
</table>
### 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'.

<table>
<thead>
<tr>
<th>Therapeutic effect</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Do not significantly interfere with patient's functioning</td>
</tr>
<tr>
<td>Marked</td>
<td>Vast improvement. Complete or nearly complete remission of all symptoms</td>
</tr>
<tr>
<td>Moderate</td>
<td>Decided improvement. Partial remission of symptoms</td>
</tr>
<tr>
<td>Minimal</td>
<td>Slight improvement which doesn't alter status of care of patient</td>
</tr>
<tr>
<td>Unchanged or worse</td>
<td>13</td>
</tr>
</tbody>
</table>

---

Laboratory Evaluations

• Routine
  – Complete blood count, comprehensive metabolic profile, UA

• Research
  – C-reactive protein (CRP)
  – Nerve growth factor
    • Eliza Assay,
  – Lincoplex human cytokine/chemokine panel
    • IL-1β, IL-6, IL-8, IL-10, IFN-γ, TNF-α,

Preliminary Results
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

<table>
<thead>
<tr>
<th>Branch</th>
<th>Number of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Army</td>
<td>33</td>
</tr>
<tr>
<td>Marine Corp</td>
<td>14</td>
</tr>
<tr>
<td>Navy</td>
<td>3</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Grouping Variable</th>
<th>Mean Diff.</th>
<th>DF</th>
<th>t-Value</th>
<th>P-Value</th>
<th>95% Lower</th>
<th>95% Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextro-Placebo, Dextro.</td>
<td>0.188</td>
<td>30</td>
<td>-0.5304</td>
<td>0.577</td>
<td>-0.416</td>
<td>0.791</td>
</tr>
<tr>
<td>Dextro-Placebo, Post-TX</td>
<td>-0.378</td>
<td>10</td>
<td>-1.416</td>
<td>0.168</td>
<td>-0.791</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Group Info for Change from Baseline
Grouping Variable: Treatment

<table>
<thead>
<tr>
<th>Count</th>
<th>Mean</th>
<th>Variance</th>
<th>Std. Dev.</th>
<th>Std. Err</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextro-Placebo</td>
<td>16</td>
<td>-0.250</td>
<td>0.333</td>
<td>0.144</td>
</tr>
<tr>
<td>Dextro.</td>
<td>16</td>
<td>-0.438</td>
<td>1.063</td>
<td>0.258</td>
</tr>
</tbody>
</table>
CGI Q#1, naltrexone vs placebo

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

<table>
<thead>
<tr>
<th>Grouping Variable: Treatment</th>
<th>Mean Diff</th>
<th>DF</th>
<th>t-Value</th>
<th>P-value</th>
<th>95% Lower</th>
<th>95% Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone, Naltrexone-Placebo</td>
<td>.123</td>
<td>40</td>
<td>.549</td>
<td>.5858</td>
<td>-.329</td>
<td>.574</td>
</tr>
</tbody>
</table>

Group Info for Change from Baseline
Grouping Variable: Treatment

<table>
<thead>
<tr>
<th></th>
<th>Count</th>
<th>Mean</th>
<th>Variance</th>
<th>Std. Dev.</th>
<th>Std. Err</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone</td>
<td>20</td>
<td>-.150</td>
<td>.661</td>
<td>.813</td>
<td>.182</td>
</tr>
<tr>
<td>Naltrexone-Placebo</td>
<td>22</td>
<td>-.273</td>
<td>.388</td>
<td>.631</td>
<td>.135</td>
</tr>
</tbody>
</table>

Laboratory Values
NGF, pg/mL

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

<table>
<thead>
<tr>
<th></th>
<th>Mean Diff</th>
<th>DF</th>
<th>t-Value</th>
<th>P-Value</th>
<th>95% Lower</th>
<th>95% Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, Naltrexone</td>
<td>15.893</td>
<td>27</td>
<td>3.159</td>
<td>.0039</td>
<td>5.571</td>
<td>26.215</td>
</tr>
<tr>
<td>Baseline, Nal-Plac</td>
<td>25.786</td>
<td>27</td>
<td>5.183</td>
<td>&lt;.0001</td>
<td>15.577</td>
<td>35.994</td>
</tr>
</tbody>
</table>

Paired Means Comparison

Hypothesized Difference = 0

<table>
<thead>
<tr>
<th></th>
<th>Mean Diff</th>
<th>DF</th>
<th>t-Value</th>
<th>P-Value</th>
<th>95% Lower</th>
<th>95% Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, Dex-Plac</td>
<td>20.867</td>
<td>14</td>
<td>2.402</td>
<td>.0308</td>
<td>2.232</td>
<td>38.501</td>
</tr>
<tr>
<td>Dex, Dex-Plac</td>
<td>6.357</td>
<td>13</td>
<td>.860</td>
<td>.9510</td>
<td>-11.945</td>
<td>24.663</td>
</tr>
</tbody>
</table>
VAS scores for sleeping problems. Significantly decreased with both naltrexone, dex, and their respective placebos.

\[
\text{Baseline, Naltrexone} & \quad 25.741 \quad 26 \quad 4.730 \quad <.0001 \quad 14.555 \quad 36.926 \\
\text{Baseline, Nal-Plac} & \quad 30.444 \quad 26 \quad 4.771 \quad <.0001 \quad 17.328 \quad 43.561 \\
\text{Naltrexone, Nal-Plac} & \quad 2.385 \quad 25 \quad .632 \quad .5332 \quad -5.387 \quad 10.157
\]

Paired Means Comparison
Hypothesized Difference = 0

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

\[
\text{Baseline, Naltrexone} & \quad 7.296 \quad 26 \quad 1.749 \quad .0921 \quad -1.279 \quad 15.872 \\
\text{Baseline, Nal-Plac} & \quad 6.556 \quad 26 \quad 1.311 \quad 2684 \quad -5.359 \quad 18.470 \\
\text{Naltrexone, Nal-Plac} & \quad -9.62 \quad 25 \quad -1.193 \quad 8488 \quad -11.242 \quad 9.319
\]

Paired Means Comparison
Hypothesized Difference = 0

\[
\text{Baseline, Dex} & \quad 18.313 \quad 15 \quad 2.796 \quad .0144 \quad 4.201 \quad 32.424 \\
\text{Baseline, Dex-Plac} & \quad 9.000 \quad 15 \quad 1.520 \quad 1493 \quad -3.652 \quad 21.623 \\
\text{Dex, Dex-Plac} & \quad -8.333 \quad 14 \quad -2.271 \quad .0584 \quad -16.203 \quad -0.464
\]

Paired Means Comparison
Hypothesized Difference = 0
**VAS scores for memory problems. Effect of naltrexone placebo and with Dex alone (but not its placebo).**

**POSITIVE FINDING!**

<table>
<thead>
<tr>
<th>Paired Means Comparison</th>
<th>Hypothesized Difference = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Diff.</td>
<td>DF</td>
</tr>
<tr>
<td>Baseline, Naltrexone</td>
<td>9.370 26</td>
</tr>
<tr>
<td>Baseline, Nal-Plac</td>
<td>11.852 26</td>
</tr>
<tr>
<td>Naltrexone, Nal-Plac</td>
<td>2.577 25</td>
</tr>
</tbody>
</table>

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

**POSITIVE FINDING!**
**VAS scores for joint pain. Nothing for either drug.**

<table>
<thead>
<tr>
<th>Paired Means Comparison</th>
<th>Hypothesized Difference = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Diff.</td>
<td>DF</td>
</tr>
<tr>
<td>Naltrexone, Nal-Plac</td>
<td>1.923</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Paired Means Comparison</th>
<th>Hypothesized Difference = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Diff.</td>
<td>DF</td>
</tr>
<tr>
<td>Baseline, Naltrexone</td>
<td>6.630</td>
</tr>
<tr>
<td>Baseline, Nal-Plac</td>
<td>10.481</td>
</tr>
<tr>
<td>Naltrexone, Nal-Plac</td>
<td>5.654</td>
</tr>
</tbody>
</table>
VAS scores for inappropriate anger. Effect with naltrexone and its placebo. Nothing with Dex or its placebo.

<table>
<thead>
<tr>
<th></th>
<th>Mean Diff</th>
<th>DF</th>
<th>t-Value</th>
<th>P-Value</th>
<th>95% Lower</th>
<th>95% Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, Naltrexone</td>
<td>14.889</td>
<td>26</td>
<td>2.328</td>
<td>.0281</td>
<td>1.730</td>
<td>28.048</td>
</tr>
<tr>
<td>Baseline, Nal-Plac</td>
<td>18.915</td>
<td>26</td>
<td>2.546</td>
<td>.0172</td>
<td>3.626</td>
<td>34.003</td>
</tr>
<tr>
<td>Naltrexone, Nal-Plac</td>
<td>4.154</td>
<td>25</td>
<td>.601</td>
<td>.5533</td>
<td>-10.081</td>
<td>18.389</td>
</tr>
</tbody>
</table>

Paired Means Comparison
Hypothesized Difference = 0

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.

<table>
<thead>
<tr>
<th></th>
<th>Mean Diff</th>
<th>DF</th>
<th>t-Value</th>
<th>P-Value</th>
<th>95% Lower</th>
<th>95% Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, Mean Nal</td>
<td>-1.432</td>
<td>26</td>
<td>-3.901</td>
<td>.0006</td>
<td>-2.187</td>
<td>-.677</td>
</tr>
<tr>
<td>Baseline, Mean Nal-Plac</td>
<td>-1.148</td>
<td>26</td>
<td>-3.217</td>
<td>.0035</td>
<td>-1.882</td>
<td>-.415</td>
</tr>
<tr>
<td>Mean Nal, Mean Nal-Plac</td>
<td>333</td>
<td>25</td>
<td>7.915</td>
<td>.4715</td>
<td>-8.066</td>
<td>1.272</td>
</tr>
</tbody>
</table>

Paired Means Comparison
Hypothesized Difference = 0

<table>
<thead>
<tr>
<th></th>
<th>Mean Diff</th>
<th>DF</th>
<th>t-Value</th>
<th>P-Value</th>
<th>95% Lower</th>
<th>95% Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, Mean Dex</td>
<td>-6.479</td>
<td>15</td>
<td>-7.459</td>
<td>&lt;.0001</td>
<td>-8.333</td>
<td>-4.625</td>
</tr>
<tr>
<td>Baseline, Mean Dex-Plac</td>
<td>-1.833</td>
<td>15</td>
<td>-4.466</td>
<td>.0006</td>
<td>-2.708</td>
<td>-.958</td>
</tr>
<tr>
<td>Mean Dex, Mean Dex-Plac</td>
<td>4.844</td>
<td>14</td>
<td>4.526</td>
<td>.0006</td>
<td>2.548</td>
<td>7.140</td>
</tr>
</tbody>
</table>

Paired Means Comparison
Hypothesized Difference = 0
Army infantry
GW age 21, in

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,

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Naltrexone visit 1</th>
<th>Naltrexone visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>joint</td>
<td>81</td>
<td>5</td>
</tr>
<tr>
<td>muscle</td>
<td>71</td>
<td>63</td>
</tr>
<tr>
<td>diarrhea</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>rash</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>memory</td>
<td>82</td>
<td>33</td>
</tr>
<tr>
<td>Sleep</td>
<td>99</td>
<td>30</td>
</tr>
<tr>
<td>concentration</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>fatigue</td>
<td>99</td>
<td>40</td>
</tr>
<tr>
<td>dizziness</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>vertigo</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>intransibility</td>
<td>99</td>
<td>38</td>
</tr>
<tr>
<td>anger</td>
<td>99</td>
<td>2</td>
</tr>
<tr>
<td>depression</td>
<td>99</td>
<td>5</td>
</tr>
</tbody>
</table>
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

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

References


References