Q10 for Gulf War Veterans:
A double-blind randomized pilot study
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Abbreviations

AChEi: acetylcholinesterase inhibitor
EN: Energetics/ bioenergetics.
GWI: Gulf War illness.
GWV: Gulf War veterans.
MD: Mitochondrial dysfunction.
Mt: Mitochondrial
OS: Oxidative stress.
PB: pyridostigmine bromide, a nerve agent pretreatment adjunct given to many GW personnel that acts as an AChEi
Q10: Coenzyme Q10 (ubiquinone)
RCT: randomized controlled trial
RFs: Risk factors
ROS: reactive oxygen species (free radicals that mediate OS)
Sx: symptoms
Mg: milligrams
Tid: three times a day
Q100: Q10 at 100mg/d
Q300: Q10 at 300mg/d
What is Rationale for Q10?

- OS: Q10 is the primary endogenous lipophilic antioxidant
- MD: Q10 bypasses many mt respiratory chain abnormalities, to improve EN.
- Q10 has been reported to reduce symptoms in MD – variably, depending e.g. on the mt defect; & degree to which not OSMD now, but consequences of OSMD like cell loss, are responsible for sx
- MD, once triggered, leads to more OS: -> cell dysfunction & cell death.
- If severe & targeting relevant tissues, these processes can trigger a vicious cycle, culminating in neurodegenerative conditions like ALS (in which these mechanisms – and some GW exposures – are implicated) – increased in GWI.
- Q10 may reduce OS, & MD, & sx arising from these now.
- Q10 will not help all sequelae like those from already dead cells (from postmitotic tissues with low replication or where satellite cell replication has been exhausted) – e.g. atrophy. Not envisaged as “cure” – as not a cure in MD.
- It will not likely unscar already ischemically scarred tissue, reverse autoimmunity once induced, or address toxicity to mito transport.
- But at favorable dose – which depends on the person –, it may help sx arising from current OS; and EN deficit from MD per se; and may retard progression from causes including some of those it will not reverse.

Methods:
Subjects: 46 GWV randomized, who meet CDC and Kansas criteria for GWI
Design:
2 week placebo run-in
Double blind, placebo-controlled crossover w 3-mo periods
Q10 100, 300, or placebo
Visits: Run-in, baseline, 3, 6, 9, & 12 mo visits

Intervention
Q10 at 0,100, or 300mg/d in divided doses (tid)
PharmaNord Q10 (myoquinone) chosen:
Excellent quality control
No stearates, titanium, other untoward ingredients
High bioavailability
High tolerance by intolerant
Existing FDA IND (Investigational New Drug status)
Everyone got 3 pills/d in two bottles. Take 1 pill from small bottle, two from large, distributed across day (tid), preferably not too close to bedtime.
Choice of Dose & Timing

Considerations:
Divided doses -> improved blood levels BUT
Evening use esp hi dose can -> “Activation Insomnia” (rev up cell energy)

We considered higher dose BUT:
a. Most antioxidants become prooxidant at “high” dose. What is “high” depends on the person. More OS tolerates higher Q10.
b. High bioavailability of this brand – higher effective dose
c. PharmaNord’s recommendation: ~100mg

Outcomes Presented

1°: GSRH
2°: Symptoms (Sx): What GWI is all about.
   Sx Score
   Individual Sx
Sx change scores used: reduce recalibration impact

ALSO:
Physiological: SBP: HTN incr in GWV*. Low BP also a risk.
Physical: SPS = Summed score of 3 items: timed # chair rises; timed balance 3 ways; 4 meter walking velocity. Each scored 0-4, max score 12.

*Unwin, 1999; Kang, 2000; Gray, 2002; McCauley, 2002; Ismail, 2007
Parallel design, 1st Phase analysis shown. Least # drops, no carryover effects. Important if bidirectional rx.

No adjustment for multiple hypotheses that are principled:
  a) Presumes chance=1st order explanation.
  b) Pilot study (type 2 error is the greater risk)

Pilot + hypoth supported by benefits in other samples: will generally present 1-sided p-values (will “stray” and give 2-sided sometimes)

Findings must rest on replication.

Rothman 1990 Epidemiology 1: 43-6 No adjustments are needed for multiple comparisons

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**Subjects:**

**Baseline Characteristics**

- **%Male:** 85%
- **Ethnicity:**
  - White 60%
  - AA 13%
  - Hispanic 13%
  - “other” 7%
  - Native Am 4%
  - Asian 2%
- **Highest Education (all HS grads):**
  - 46% some college
  - 28% college grad
  - 15% masters
  - 2% doctorate
- **Branch:**
  - Army 24%
  - Marines 35%
  - Navy 37%
  - Air Force 4%
- **Enlisted:** 85%; **Officer:** 15%
- **Health Before Gulf:**
  - Excellent 74%
  - Very Good 21%
  - Good 2%
  - Fair 2%
  - Poor 1%
- **Health Now:**
  - Excellent 2%
  - Very Good 4%
  - Good 22%
  - Fair 56%
  - Poor 15%
Baseline: Top 20 Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACHES-PAINS</td>
</tr>
<tr>
<td>JOINT PAIN</td>
</tr>
<tr>
<td>TIRED</td>
</tr>
<tr>
<td>SLEEP PROBLEMS</td>
</tr>
<tr>
<td>GO BACK RECHECK THINGS</td>
</tr>
<tr>
<td>MUSCLE PAIN</td>
</tr>
<tr>
<td>WORD RECALL PROBS</td>
</tr>
<tr>
<td>IRRITABILITY</td>
</tr>
<tr>
<td>IMPATIENCE</td>
</tr>
<tr>
<td>ATTENTION/ CONC. PROBS</td>
</tr>
<tr>
<td>INAD. ENERGY TO START THGS</td>
</tr>
<tr>
<td>HEADACHE</td>
</tr>
<tr>
<td>ANXIETY</td>
</tr>
<tr>
<td>MUSCLE FATIGUE</td>
</tr>
<tr>
<td>FATIGUE W EXERTION</td>
</tr>
<tr>
<td>RINGING EARS</td>
</tr>
<tr>
<td>zRECALL WHR GOING/WHAT DOING</td>
</tr>
<tr>
<td>DRY SKIN</td>
</tr>
<tr>
<td>COLD HANDS &amp; FEET</td>
</tr>
<tr>
<td>READING COMPREHENSION TROUBLE</td>
</tr>
</tbody>
</table>

Baseline: Key Measures

<table>
<thead>
<tr>
<th>Msr</th>
<th>Mean± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSRH</td>
<td>2.2 ± .84</td>
<td>1-5*</td>
</tr>
<tr>
<td>SBP</td>
<td>123 ± 15</td>
<td>97-181.5 (LOW to HIGH)</td>
</tr>
<tr>
<td>SPS</td>
<td>10.0 ±1.69</td>
<td>0-12 (almost max)</td>
</tr>
</tbody>
</table>

GSRH = single item general self-rated health
*Poor, Fair, Good, Very Good, Excellent
SBP = systolic bp (mm Hg)
SPS = summary performance score
**GSRH: Primary Provisional**

Rated Poor, fair, good, very good, excellent (5-point scale)

Examined change *from run-in*

Baseline around 2 (fair), so ~3 points poss

<table>
<thead>
<tr>
<th></th>
<th>Chg</th>
<th>SD</th>
<th>1-sided P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo:</td>
<td>+.32</td>
<td>.32</td>
<td>--</td>
</tr>
<tr>
<td>Q100:</td>
<td>+.70</td>
<td>.82</td>
<td>0.12</td>
</tr>
<tr>
<td>Q300:</td>
<td>+.60</td>
<td>1.1</td>
<td>0.21</td>
</tr>
<tr>
<td>Q:</td>
<td>+.65</td>
<td>.93</td>
<td>0.12</td>
</tr>
</tbody>
</table>

So the direction of difference is favorable, but the change is not significant.

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**Symptom Score**

Cannot improve a sx that isn’t present.

Thus, target Sx present in at least 50%: N=20 sx (so, present in at least 23 at baseline)

*These sx are balanced at baseline Q100 v placebo*

Create Symptom Score:

- Sum effect across sx present (top 20 sx) (-2 to +2).
- Divide by # sx for that person.

Compare Mean Effect Per Sx:

- Placebo  +0.083 (± .42) (more sx)
- Q10 100  - 0.32 (± .57) (less sx)

1-sided P = 0.016

∴ Q10 100mg benefits sx in GWI
Direction of Sx Change Individually:
Null Hypothesis Expectation: half the sx trend better, half trend worse.
Finding: 20 out of 20 better on Q100
Likelihood by chance (2-sided):
1/2^{19}: p<0.000001
Provides (further) rationale for use of 1-sided p-values for indiv sx.

Individual Symptoms
RX1: 1-sided P-values.

<table>
<thead>
<tr>
<th></th>
<th>Q100</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>-.66</td>
<td>&lt; +.13</td>
<td>.0019**</td>
</tr>
<tr>
<td>AttnxPrb</td>
<td>-.5</td>
<td>&lt; +.13</td>
<td>.023*</td>
</tr>
<tr>
<td>Energy2do</td>
<td>-.44</td>
<td>&lt; +.13</td>
<td>.046</td>
</tr>
<tr>
<td>Impatient</td>
<td>-.5</td>
<td>&lt; +.18</td>
<td>.048</td>
</tr>
<tr>
<td>Ringears</td>
<td>-.25</td>
<td>&lt; +.25</td>
<td>.054</td>
</tr>
<tr>
<td>Dryskin</td>
<td>-.5</td>
<td>&lt; +.5</td>
<td>.041</td>
</tr>
<tr>
<td>Tired</td>
<td>-.3</td>
<td>&lt; +.06</td>
<td>.05</td>
</tr>
</tbody>
</table>

RECALL: “-” is lessening of sx
**SYMPTOMS**

RX1: 1-sided P.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Q100</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>-.71</td>
<td>&lt; 0</td>
<td>.067</td>
</tr>
<tr>
<td>Trblrec</td>
<td>-.43</td>
<td>&lt; -.07</td>
<td>.09</td>
</tr>
<tr>
<td>Readcomp</td>
<td>-.5</td>
<td>&lt; 0</td>
<td>.097</td>
</tr>
<tr>
<td>Slprb</td>
<td>-.5</td>
<td>&lt; 0</td>
<td>.10</td>
</tr>
<tr>
<td>Irritable</td>
<td>-.29</td>
<td>&lt; +.16</td>
<td>.10</td>
</tr>
<tr>
<td>Msclpn</td>
<td>-.1</td>
<td>&lt; +.23</td>
<td>.14</td>
</tr>
<tr>
<td>Memtask</td>
<td>-.33</td>
<td>&lt; +.08</td>
<td>.17</td>
</tr>
</tbody>
</table>

RECALL: “-” is lessening of sx

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**Headache**

Baseline: HA balanced across arms

Treatment:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean</th>
<th>1-sided P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>+.13</td>
<td></td>
</tr>
<tr>
<td>Q100</td>
<td>-.67</td>
<td>.002</td>
</tr>
<tr>
<td>Q300</td>
<td>-.5</td>
<td>.03</td>
</tr>
<tr>
<td>Q</td>
<td>-.57</td>
<td>.0049</td>
</tr>
</tbody>
</table>

Extends prior finding of benefit to migraine (on 100mg tid)

**Diarrhea**

Not in the top 20sx: but GI sx are in Kansas criteria and this was the most common GI sx.

Baseline comparable
- Placebo: .36 (SD .49); Q100: .36 (SD .50)

Treatment Effect:
- W/o adjustment for baseline: p = 0.045 1-sided
- Ologit adjusted for baseline diarrhea rating:
  - Beta = -.27 (SD 1.34)
  - 1-sided P: 0.022

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**SBP (mmHg) on Q10 100**

Normalize low ~& high SBP?

<table>
<thead>
<tr>
<th>Treatment Gp</th>
<th>Placebo</th>
<th>100mg Q10</th>
<th>Diff</th>
<th>1-sided P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low SBP: &lt;120</td>
<td>-6.9 (7.8)</td>
<td>+7 (10.4)</td>
<td>+14</td>
<td>0.0044</td>
</tr>
<tr>
<td>High SBP: &gt;125</td>
<td>-13 (16.3)</td>
<td>-23 (12.8)</td>
<td>-10</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Q10 300mg: No relationship
Q10 approved in Japan for CHF; poor heart pumping a factor in low BP
Q10 benefits high BP in prior meta-analysis*

Primary Q10 AE: Sleep Prb

Sleep problems direction: Better Q100, worse Q300:

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>P (vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
<td>.71</td>
<td></td>
</tr>
<tr>
<td>Q100</td>
<td>-0.5</td>
<td>1.2</td>
<td>.05</td>
</tr>
<tr>
<td>Q300</td>
<td>+.63</td>
<td>.74</td>
<td>.025 (2-sided)</td>
</tr>
</tbody>
</table>

100 vs 300 (same means) .02

Logit adj baseline sleep problems:
Q300 $\beta$ 2.3, SE 1.0., p = 0.012
(regress slpprb on Q300 & baseline: $\beta$.78 (.30) 0.008)

Sleep Mediates Q300 Probs that were Seen w Some Sx

<table>
<thead>
<tr>
<th></th>
<th>Sleep alone</th>
<th>Q3 alone</th>
<th>Q3 adj sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recheck</td>
<td>+***</td>
<td>+*</td>
<td>Ø</td>
</tr>
<tr>
<td>Jtpain</td>
<td>Ø</td>
<td>Ø</td>
<td>-3.0*</td>
</tr>
<tr>
<td>ReadComp</td>
<td>+**</td>
<td>+2.4*</td>
<td>-1.6</td>
</tr>
<tr>
<td>Musclpn</td>
<td>+**</td>
<td>-1.3</td>
<td>-2.7*</td>
</tr>
<tr>
<td>Impatient</td>
<td>+****</td>
<td>+**</td>
<td>Ø</td>
</tr>
<tr>
<td>Energy</td>
<td>+****</td>
<td>+*</td>
<td>Ø</td>
</tr>
<tr>
<td>Headache</td>
<td>+**</td>
<td>-1.7*</td>
<td>-2.5*</td>
</tr>
<tr>
<td>Memtask</td>
<td>+****</td>
<td>+***</td>
<td>Ø</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>+*</td>
<td>Ø</td>
<td>-1.6</td>
</tr>
</tbody>
</table>

Ologit analyses adjusted for baseline
*≤ 0.1  **≤0.05  ***≤0.01  ****≤0.001
Physical Fxn

SPS: Sum of: 1) timed # chair rises; 2) timed balance 3 ways; 3) 4-meter walking velocity. Each scored 0-4, max score 12.

SPS: higher score, or + change, is better.

Designed for elderly: Not much room to improve (baseline ave 10 on 12 point scale)

Placebo: +0.5 (SD 1.2)
Q100: + 1.1 (SD .83)

Q100: 73% improved, 0% worse (rest no change)
Placebo: 35% improved, 15% worse (rest no change)

1-sided P = .05 (chi-squared)

(Fatigue w Exertion)

Cross-over design in general a problem given nonmonotonic Q10 effects (+ use of change). Analyzed for this vbl tho:

Q100 vs Placebo, 1-sided P-values

<table>
<thead>
<tr>
<th></th>
<th>T-test</th>
<th>Sign Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vs Placebo 1</td>
<td>.0003</td>
<td>.0005</td>
</tr>
<tr>
<td>Vs Placebo 2</td>
<td>.0088</td>
<td>.016</td>
</tr>
</tbody>
</table>

Every person whose change score differed btn Q100 and placebo – against each placebo – did better on Q100.

11:0 and 6:0. (just over half reported fatigue w exertion.)

Q100 also superior to Q300 (p = 0.0195)
**Discussion:**

**Dose Consideration**

Nonmonotonic.
This is the norm for antioxidants: many are prooxidant at higher doses. BUT point of transition varies.

This is common for nutrients: Supplement trials often err by thinking if some is good, more is better*


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**Limitations**

1. Small Sample: But some key findings sig
2. Short Duration: But some key findings sig
3. Switch to 1st phase parallel design: but strengthens authority given carry-over
4. Findings: Require replication
5. Analyses not yet complete
# Conclusions

1. PharmaNord Q100 significantly benefited leading symptoms on average in GWV with GWI.
2. Q300 did not benefit sx score on average. It led to sleep problems & (apparently “via” this) was unfavorable on some sx. Can’t distinguish dose per se, vs proximity to bedtime.
3. Q100 separately, significantly benefited headache & attention + benefit or trend for other sx including fatigue, mood/personality, autonomic, skin, muscle (+ GI). Direction vs placebo=favorable for all.
4. Fatigue w Exertion: A key issue given the salience of exercise to sleep, cognition, muscle fxn, pain, mood (and BP!). Need ability to exercise. Exercise and/or ex tolerance protects vs heart, cancer, dementia; & improves outcomes in illness, injury, surgery etc.

## Implications

Though study is small, and findings must be viewed as provisional, these findings support widespread benefits of Q10 at 100mg/d, modest but material in magnitude, across numerous symptoms and domains of relevance to GWV.

They support the need for a carefully conducted larger scale study to replicate & extend these findings, using – as here – a high quality, high bioavailability coQ10 preparation.
Thank You