Q10 for Gulf War Veterans:

A double-blind randomized pilot study

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Abbreviations

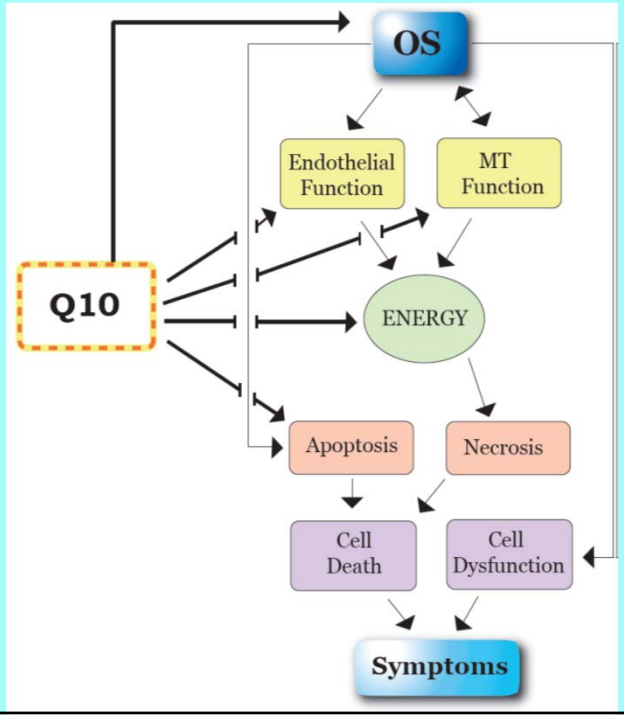
AChEi: acetylcholinesterase inhibitor
EN: Energetics/ bioenergetics.
GWI: Gulf War illness.
GWV: Gulf War veterans.
MD: Mitochondrial dysfunction.
Mt: Mitochondrial
OS: Oxidative stress.
PB: pyridostigmine bromide, a nerve agent pretreatment adjunct given to many GW personnel that acts as an AChEi
Q10: 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.**

Linnane AW, Zhang C, Yarovaya N, et al. Human aging and global function of coenzyme Q10. Ann N Y Acad Sci 2002;959:396-411; discussion 63-5.

Sastre J, Pallardo FV, Vina J. The role of mitochondrial oxidative stress in aging. Free Radic Biol Med 2003;35:1-8.



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

Subjects:
Baseline Characteristics

%Male: 85%

Ethnicity: White 60% AA 13% Hispanic 13%
"other" 7% Native Am 4% Asian 2%

Highest Education (all HS grads): 9% tech school;
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

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

Baseline: Key Measures

Msr	Mean± SD	Range
GSRH	2.2 ± .84	1-5*
SBP	123 ± 15 “normal”	97-181.5 (LOW to HIGH)
SPS	10.0 ±1.69	0-12 (almost max)

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

	Chg	SD	1-sided P
Placebo:	+.32	.32	--
Q100:	+.70	.82	0.12
Q300:	+.60	1.1	0.21
Q:	+.65	.93	0.12

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

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.

	Q100		Placebo	P
Headache	-.66	<	+.13	.0019**
AttnxPrb	-.5	<	+.13	.023*
Energy2do	-.44	<	+.13	.046
Impatient	-.5	<	+.18	.048
Ringears	-.25	<	+.25	.054
Dryskin	-.5	<	+.5	.041
Tired	-.3	<	+.06	.05

RECALL: "-" is lessening of sx

SYMPTOMS

RX1: 1-sided P.

	Q100	Placebo	P
Anxiety	-.71	< 0	.067
Trblrec	-.43	< -.07	.09
Readcomp	-.5	< 0	.097
Slprb	-.5	< 0	.10
Irritable	-.29	< +.16	.10
Msclpn	-.1	< +.23	.14
Memtask	-.33	< +.08	.17

RECALL: "-" is lessening of sx

Headache

Baseline: HA balanced across arms

Treatment:

	Mean	1-sided P
Placebo	+.13	
Q100	-.67	.002
Q300	-.5	.03
Q	-.57	.0049

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

Sandor PS, Di Clemente L, Coppola G, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology 2005;64:713-5.

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

SBP (mmHg) on Q10 100 Normalize low ~& high SBP?

Treatment Gp	Placebo	100mg Q10	Diff	1-sided P
Low SBP: <120	-6.9 (7.8)	+7 (10.4)	+14	0.0044
High SBP: >125	-13 (16.3)	-23 (12.8)	-10	0.19

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*

***Rosenfeldt et al. J Hum Hypertens 2007;21:297-306.**

Primary Q10 AE: Sleep Prb

Sleep problems direction: Better Q100, worse Q300:

	Mean	SD	P (vs placebo)
Placebo	0	.71	
Q100	-0.5	1.2	.05
Q300	+.63	.74	.025 (2-sided)
100 vs 300 (same means)			.02

Logit adj baseline sleep problems:

Q300 β 2.3, SE 1.0., p = 0.012

(regress slpprb on Q300 & baseline: β .78 (.30) 0.008)

Sleep Mediates Q300 Probs that were Seen w Some Sx

Relates to a number of sx:

	Sleep alone	Q3 alone	Q3 adj sleep
Recheck	+***	+*	∅
Jtpain	∅	∅	-3.0*
ReadComp	+**	+2.4*	-1.6
Musclpn	+**	-1.3	-2.7*
Impatient	+****	+**	∅
Energy	+****	+*	∅
Headache	+**	-1.7*	-2.5*
Memtask	+****	+***	∅
Dry Skin	+*	∅	-1.6

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

	T-test	Sign Test
Vs Placebo 1	.0003	.0005
Vs Placebo 2	.0088	.016

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*

***Morris MC, Tangney CC. A potential design flaw of randomized trials of vitamin supplements. JAMA 2011;305:1348-9.**

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 Q*100* significantly benefited leading symptoms on average in GWV with GWI.
2. Q*300* 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