Presentation 9 – Robert Haley

Approaches for Assessing Treatments for Gulf War Illnesses

The UT Southwestern Experience

Robert W. Haley, M.D.
Howard K. Gershenfeld, MD, PhD
Ann Matt Maddrey, PhD
UT Southwestern Medical Center
Dallas, Texas

Prerequisite Reading

- Golomb BA, Chadwick A. *Treatment considerations for ill Gulf War veterans*. RAC Technical Report. 2001.
- *Gulf War Veterans: Treating Symptoms and Syndromes*. Committee on Identifying Effective Treatments for Gulf War Veterans' Health Problems. Board on Health Promotion and Disease Prevention. Rosof BM, Hernandez LM, Editors. Institute of Medicine, Washington DC: National Academy Press. 2001.
- Cook DJ. Randomized trials in single subjects: the N of 1 study. *Psychopharm Bull* 1996;32:363-7.

Two Ways to Find Treatments for a Disease

- **Empirical Approach**
  - Screening for existing treatments that appear to work
  - Clinical trials of these promising treatments
- **Rational Approach**
  - Understand the disease pathophysiology
  - Develop medications to attack specific disease mechanisms
  - Phase I, Phase II, Phase III, Phase IV clinical trials

Two Ways to Find Treatments for a Disease

- **Empirical Approach**
  - Screening for existing treatments that apear to work
    - **Kang included screening questions on VA national survey.**
    - **UT Southwestern/RTI survey includes similar questions.**
  - Clinical Trials of treatments that appear to work
    - **VA-sponsored trials of doxycycline and CBT/exercise**
    - **Clinical trial of detoxification (Hyman et al, unpublished)**
    - **Trials of treatments for non-GW multisymptom illness (Golomb)**
- **Rational Approach**
  - Understand the disease pathophysiology
    - **UT Southwestern/Duke/Kansas State/EPA study initiated the niche of neurophysiologic studies of chemical combinations**
    - **UT Southwestern mouse models underway**
  - Develop medications to attack specific disease mechanisms
  - Phase I, Phase II, Phase III, Phase IV clinical trials

Published Clinical Trials of Treatments for CMI in Gulf War Veterans, 1999-2001

Intervention	Centers	Subjects	Outcome	Duration	Cost	Result
CBT/Exercise	20	1,092 Fukuda def PCS <41	PCS (SF-36) 7+ unit increase Power = 0.95 Alpha (corrected) = 0.008 For 15% v 30% v 45%	2-1/2 y	$12M	Negative on primary end point Small effects on secondary
Doxycycline	28	591 Fukuda def PCS <41 Mycoplasma DNA +	PCS (SF-36) 7+ unit increase Power = 0.95 Alpha = 0.05 For 15% v 30%	2-1/2 y	$12M	Negative on all end points

Design Features to Decide Before Undertaking Empirical Treatment Trials

- Case definition of illness group(s)
- What therapies or medications to test
- How rapid is the treatment's onset of action
- Trial design (simple experiment, repeated measures, n-of-1)
- Duration of treatment
- Dose to use and whether to adjust dose during study
- Outcome measure(s) (subjective vs objective; primary vs secondary)
- Variance of the outcome measure(s) and stability over time
- Size of the treatment effect to expect
- Statistical comparison of interest

Randomized Clinical Trial in a Single Subject "N-of-1 RCT"

- Most common approach
  - Patient undergoes pairs of treatment periods.
  - In each pair, one period is drug, the other placebo or alternative drug.
  - The order of the two periods is randomized within the pair.
  - Outcomes are measured at end of each period, often by a patient diary or standardized scale.
  - Multiple pairs are required to establish drug effect, harm or no effect on outcomes.
  - Analysis is often graphical with visual inspection for apparent effects.

Randomized Clinical Trial in a Single Subject "N-of-1 RCT"

- Shares many attributes with traditional crossover trials.
  - N-of-1 trials attempt to establish effects in an individual.
  - Crossover trials, in groups.
- Either can be analyzed like the other
  - Crossover trials can be analyzed for individual effects (but imprecise)
  - N-of-1 trials of many individuals can be combined to estimate group effects of the drug(s).

Randomized Clinical Trial in a Single Subject "N-of-1 RCT"

- Commonly used in the past
  - For determining best treatment for an individual
  - For early testing of new drugs in psychopharmacology
- Uses (similar to small FDA phase I trials)
  - To screen for promising drugs
  - For determining the best dose
  - For discovering adverse effects
  - To identify which end points are most affected by drug
  - Provides vital information for designing large RCTs

When is an N-of-1 Trial Useful/Feasible?

- For treatment of chronic diseases
- For patients who are highly motivated.
- For treatments with rapid onset and offset.
- When treatment trial period can be short (weeks).
- When a clinically relevant target can be measured.
- Must have a clinical trial setting with a pharmacist and psychologists, etc., to measure outcomes.

UT Southwestern Treatment Pilot Study 1997-1999

- Six medications, *at fixed safe doses*, were compared.
  - **Donepezil (Aricept)**, fixed dose 5 mg po qHS
    - An AChE-inhibitor "cognitive enhancer" approved for AD
  - **Paroxetine (Paxil)**, fixed dose 20 mg po qAM
    - An SSRI antidepressant with rapid onset and offset—dep/anx.
  - **Zolpidem (Ambien)**, fixed dose 10 mg po qHS
    - An imidazopyridine "sedative-hypnotic" approved for insomnia
  - **Lorazepam (Ativan)**, fixed dose 0.5 mg po BID
    - A benzodiazepine approved for anxiety
  - **Pindolol (Visken)**, fixed dose 5 mg po BID
    - A beta-blocker, serotonin antagonist approved for HTN but reduces irritability and impulsivity in organic brain syndrome
  - **Placebo**
    - Included to measure variance of change in outcome not due to drugs

UT Southwestern Treatment Pilot Study 1997-1999

- Enrolled 14 ill GW veterans from prior studies
  - 3 with Syndrome 1
  - 8 with Syndrome 2
  - 3 with syndrome 3
- Initial evaluation after week of study testing in GCRC
  - H&P and routine blood testing
  - Interview by the project psychiatrist for suitability
  - Informed consent obtained and instructions given
  - Subjects' medications studied for interactions with study drugs; contraindicated drugs were deleted for that patient

UT Southwestern Treatment Pilot Study 1997-1999

- Multi-Subject N-of-1 design with 6 medication blocks
- Each medication block lasted 4 weeks.
- Two-week baseline/washout period at start and after each block.
- Design: p**AA**p**BB**p**CC**p**DD**p**EE**p**FF**p p=placebo
- Drug order was randomly assigned.
- Subjects took two identical capsules qAM and qHS, compounded by a specialized clinical trials pharmacist.
- A "blinded" psychologist measured outcomes every two weeks.
- Study cost $250,000 funded by Perot Foundation.
- Duration 9 months.

UT Southwestern Treatment Pilot Study 1997-1999

- Primary outcome measurements
  - A psychologist interviewed the subject and spouse at the end of every 2-week assessment period.
  - Primary outcome measure: Clinical Global Impression (CGI), a standard outcome of psychopharmacology trials.
    - Veteran's self-rating compared with his condition at start of trial
    - 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse
    - A change of 2 points is considered a clinically important change.
  - After interviewing veteran and spouse, the psychologist recorded her own assessment of the CGI.
  - Assessed drug side effects.

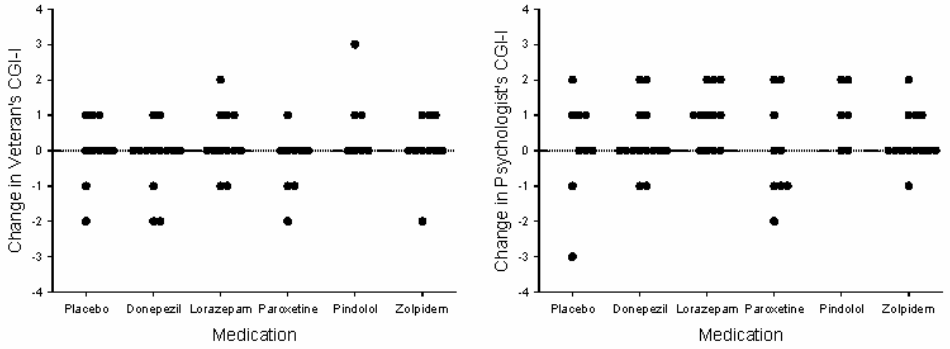
UT Southwestern Treatment Pilot Study 1997-1999

- Secondary outcome measurements
  - Veterans filled out and mailed the following standardized measures:
    - SF-36
    - Symptom Checklist-90-R (SCL-90-R)
    - Neuropsychological Impairment Scale (NIS)
    - Beck Depression Inventory (BDI)
    - Beck Anxiety Inventory (BAI)
    - Social and Occupational Functioning Assessment (SOFA)
  - Spouse filled out and mailed:
    - Scales of veterans' specific symptoms
  - Purpose of the secondary measures was to identify specific symptoms responsible for changes in primary outcome CGI.

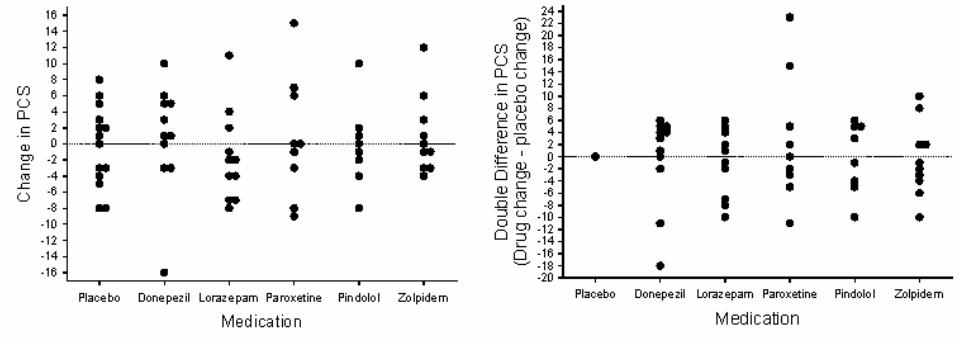
UT Southwestern Treatment Pilot Study 1997-1999

- Statistical analysis
  - Graphical analysis of difference between baseline and block value of:
    - Primary outcome, Veteran's CGI
    - Psychologist's CGI
    - Other secondary outcomes
  - Graphical analysis of "double difference" – the baseline-drug difference of the drug block minus the baseline-drug difference of the placebo block.
  - Univariate and multivariate linear regression analysis of predictors of the primary outcome, veteran's CGI score
    - Determine which secondary outcomes best predicts the primary outcome.

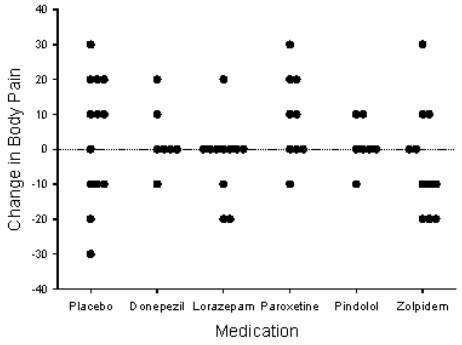
Results, Primary Outcome

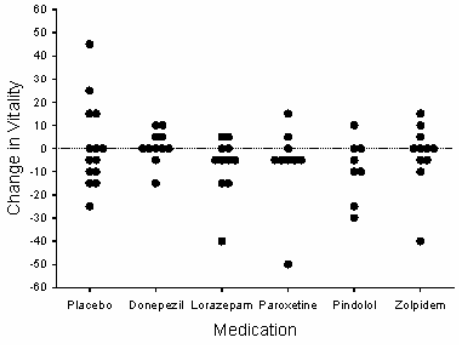


Results, Secondary Outcomes



Results, Secondary Outcomes





Linear Regression Analyses of Veteran's CGI Scores

Controlling for subject and time effects.

Psychologist's CGI and SOFAS not included.

Model $R^2 = 0.44$

Table 2. Secondary measures that best predict the veteran's changing CGI-I scores in univariate and multivariate linear regression analyses controlling for veterans and time.

Explanatory measure	Univariate association* F(1,174)	p	Multivariate model† Adj F	p
Psychologist's CGI-I measure of change	74.2	<0.0001		. . .‡
Social & Occupational Function (SOFAS)	30.8	<0.0001		. . .‡
Short Form-36 (SF-36)				
Physical Component Score	13.4	0.0003		
Body Pain	37.3	<0.0001	36.9	<0.0001
Physical Functioning	15.0	0.0002		
General Health	6.4	0.01		
Role Physical	9.4	0.003		
Mental Component Score	9.3	0.003		
Vitality	13.8	0.0003	5.9	0.017
Social Functioning	9.9	0.002		
Role Emotional	12.4	0.0005		
Mental Health	6.7	0.01		
Beck Scales				
Beck Depression Scale	9.4	0.003		
Beck Anxiety Scale	10.4	0.002		
Neuropsychological Impairment Scale (NIS)§				
Global Measure of Impairment	5.1	0.03		
Symptom Intensity Measure	9.3	0.003	4.1	0.043
Frustration Tolerance Subscale	6.2	0.01		
Critical Items of Neurologic Illness	7.8	0.006		
Affective Disturbance	7.2	0.008		
Symptom Checklist-90-R (SCL-90-R)¶				
Global Severity Index	17.8	<0.0001		
Positive Symptom Distress Index	17.9	<0.0001		
Somatization (bodily dysfunction)	22.3	<0.0001		
Depression	14.0	0.0003		
Obsessive-Compulsive	9.2	0.003		
Anxiety	4.6	0.03		
Medication side effects	2.2	0.13	4.1	0.047

Conclusions

- None of the drugs appeared to improve CGI over 4 weeks. Possible trends for PCS.
- If the CGI measure of veterans' own impression of improvement is a good measure of outcome,
  - It appears to be affected most by the Body Pain and Vitality measures of SF-36, symptom intensity, and medication side effects.
  - But not by Physical or Mental Component Scores, Beck scales, or psychological conditions.
- Main drawbacks
  - Did not determine optimal or maximal tolerated doses.
  - Performed on only one block for each drug.

Issues to Address Next Time

- Conduct an unblinded run-in period before starting the trial to:
  - Determine the optimal dose.
  - Eliminate drugs with no effect or intolerable side effects.
- Consider a treatment clinic to do unblinded N-of-1 treatment to identify promising treatments for each symptom.
- Further analyses of CGI vs PCS
- Use syndrome variant/exposure case definitions to obtain groups with homogeneous illness.
- Consider treating all depression with SSRI before enrollment.
- Consider objective outcomes such as fMRI.
- Select promising drugs suggested by surveys.
- Test drugs on animal models.

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