

ALS/MND Meeting
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Summary of Highlights
By Robert G. Miller, M.D.
Director, Forbes Norris MDA/ALS Research Center

Alternative Medicine Overview

Stephen Barrett, Quackwatch.org, Allentown, PA

Barrett listed 21 websites and 3000 pages of news on unscientific methods on his website (quackwatch.org). On Quackwatch.org, Barrett reports Eisenberg's published paper claims that 1 out of 3 Americans use alternative methods of treatment; this is not true but alternative treatments have caught on in a major way. Alternative treatments include exercise or self help groups. The phrase "alternative treatment methods" is now used for any nonstandard therapy which includes 1) legitimate choices of care (such as acupuncture for pain) 2) experimental choices (for example, Ornish diet), 3) questionable treatments (quackery, homeopathy-that small amount of something that produces desired results, nonsense). The accrediting agencies (e.g. offering courses with nonsense alternative treatments in accredited meetings and/or medical schools) are unwilling to scrutinize these treatments. Generally journals do not have **much** impact on the public. With the internet boom, 10 short internet articles have more impact than one journal article—which is unlikely to be read by the public. However many articles on the web are slanted in favor of a treatment and thus provide an unbalanced view.

Position statements and guidelines for alternative therapies would be very helpful. The Swiss Cancer League publishes excellent papers but they are only available to a limited audience. The American Cancer Society has some papers on their websites but they are not easy to find. The internet is a great source and resource and we need to use it more often. However, most sites are commercial sites that are profiting and do not contain critical information. NIH is soft on quackery and is generally very conservative. National Institute of Complementary and Alternative Medicine is of no help; they will not tell you what works and what does not. As a result, millions of dollars are being spent on alternative treatment and yet no summary statements or reviews are being issued.

What can we do to make medicine more transparent? 1) Give out sources of information, 2) Encourage organizations to issue position papers on alternative medicine, 3) Assemble anecdotal reports (e.g. stem cells outcomes), 4) Distribute networked information, 5) Link to a free newsletter weekly at the top of Quackwatch.org, and 6) Find discussion/news/chat groups to listen and give advice. One way to reach the public could include putting out articles for the public for free with physician statements regarding quackery. Another way to combat quackery is to give patients handouts.

Conclusion: 1) Provide sound information to patients with referral to reliable sources, 2) drive patients to reliable internet sources, and 3) bad health information is like garbage, it is always there.

Phenotypic variation(difference in part of the body affected) in ALS

Professor Nigel Leigh, UK:

Pathology: Nerve cells have ubiquitin inclusions (distinctive material in the nerve cell) with loss of motor neurons. These changes are the hallmark of ALS.

There is a diagnostic delay of ALS by 12-15 months, due to delayed evaluation of patients.

Regional phenotypes: 1) Patients with marked arm weakness survive longer, male:female distribution is 9:1. Rosenfeld described onset with flail legs as slow progressive and ascending. Wokke, in his study of progressive muscular atrophy (a cousin of ALS), described a better prognosis for patients with symptoms in one arm. Cognitive changes in ALS stem from frontal lobe impairment in 10-50% of people with ALS. These patients exhibit lack of empathy, planning, and may display inappropriate behavior; cases of muscular atrophy in ALS are 5-40%. Patients with frontal impairments show white matter atrophy in the fronto-temporal regions. Sensory changes were documented first in 1929. 1/350 pts with ALS have axonal polyneuropathy (sensory loss in the feet). The El Escorial clinical diagnostic criteria do predict pathological diagnosis at autopsy (Forbes et al 2001).

Clinical Trial Results

Creatine

Dr. Jeffrey Rosenfeld, Carolinas, USA, spoke about the creatine trial. Creatine regenerates ATP. The loading dose was 5 grams of creatine per day. The maintenance dosage was increased to 10 grams per day. Endpoints of the trial were the MVIC (Maximum Voluntary Isometric Contraction) slope; fatigue, FVC (forced vital capacity), ALSFRS and SF12.

Results: The mean ALSFRS score was 36 and Vital Capacity was 77% at baseline. 13 persons who took creatine had adverse events compared to 17 persons who took placebo. 2 deaths occurred in patients who took creatine compared to 6 deaths in patients who took placebo. There was no benefit of creatine according to the ALSFRS and the MVIC slope. The question remains: were there selective responders. Overall, fatigue did not change dramatically over time. Was the creatine dose high enough? Some people were using up to 25 grams per day. Patients were asked to exercise to their limit. The exercise data has not yet been analyzed.

Drug selection trial: minocycline and creatine vs. celecoxib and creatine

Paul Gordon, Columbia, USA, is recruiting for a drug selection trial; it may take up to 10 years to develop a drug before it is available on the market (e.g. minocycline). Traynor et al. listed dozens of neuroprotective agents in their publication. Gordon will pool and test these agents for this trial. Bromberg's publication of 2005 noted that 20 or more drugs that treat symptoms are available. This new trial will be a phase II trial; it will compare what is available to emerging agents. By using ranking and selection trials, researchers will pick the best drugs out of a group of drugs, using a small sample size (only a few patients) to test the drug. Therapies will be stopped early and a winner declared.

This selection trial begins with a combination of 2 medications (minocycline and creatine vs. celecoxib and creatine). The 6 months' change in ALSFRS will be used as a primary indicator.

120 patients will be enrolled in groups of 60. After this first pool, the study will be stopped, if the mean difference is $.75SD$ (standard deviation) and if a 20% improvement occurs.

Dr. Gordon has 2 aims: safety and tolerability. Multiple agents will be tested in 60 patients. The study will have 2 groups of patients (2 arms). The goal of this trial is to get winners. There is an 80% chance of finding the right drug combination in a maximum of 120 patients.

Conclusion: Use ranking and selection to compare drug combinations and select the most promising. Statistical efficiency increases with more arms in study.

Futility

Dan Moore, Forbes Norris Center, USA, spoke on a novel design for ALS clinical trials designed to screen new drugs, termed a futility trial. Drugs that are harmful or clearly not helpful can be quickly eliminated. Design a 1 arm study where every single patient receives drug. Historical controls will be used in a 3 month lead in. If one accepts a type 1 error of 10%, one can use a smaller sample size (fewer patients).

Fast progressors

For a screening trial, De Carvalho, Portugal, is using a lead in of 3 months (no medication or placebo given) with 57 rapidly progressing consecutive patients participating. Inclusion criteria for “fast progressors” include people outside the 80th percentile of ALSFRS slope. The average progression of decline in ALSFRS was 2%/month; the mean standard deviation (sd) =9%. A typical fast progressor showed an average progression rate of >8.78%/mo, >29 at entry, with mean disease duration of 8.3 months (range 2-20 months), and Vital Capacity (VC) >60% .
Conclusion: ALSFRS with a 3 months lead in period can select fast progressors. This is a good target for screening trials. De Carvalho will send slides to those who are interested.

Predicting Rate of Disease Progression Using Percent Of Predicted Normal Strength in ALS Clinical Trial Design

Pat Andres

Maximal Voluntary Isometric Contraction data were converted to percent of predicted normal (PPN) using a regression equation based on age, gender, height and weight. This can be used for both strong and weak muscles.

QUALITY OF LIFE SESSION

O’Boyle, Ireland, presented on quality of life.

Personal concept of quality of life sees each person trying to make sense out of self and the world by achieving balance between orderly and disorderly systems (eg Nelson Mandela). It is an ideographic research. A schedule for the Evaluation of an Individual Quality of Life is used for this research. By this measurement, quality of life is what the person says it is. It is very much individual in nature and often it weighs individual concepts and constructs to make a judgment. Areas or cues of importance to each person (eg health, religion, work, family, and money) can weigh heavily on their individual concepts of quality of life. Reliability and validity can be assayed. Paradigms play an important role in quality of life (i.e. the sun is not the center of the universe). It has been shown that health status is not the same as quality of life. For

example, ALS patients are more impaired than post polio syndrome and multiple sclerosis patients and yet the seiqol (Quality of Life) is the same.

The response shift shows an increased quality of life even while disease is progressing. However, changes in coping, values, social dynamics, etc., are evident. This can be used as a model. Usually, staying in control is the key for many patients. Karolinska developed a computerized version of seiqol (Quality of Life measure). Seiqol is an intervention that helps people think and process what is happening to patients.

Claffey, an Occupational Therapist, spoke of affirming life and preparing for death. Meaningful occupation has a direct correlation to wellness. Volition helps us act in behaviors that are valuable (control and spirituality are important). Diseases can present constraints that discourage work; in this case, changing habits and environment can be a big help. Positive alliances, emotional proximity (too near vs far and dependency), ability to tolerate chaos, experience loss (letting go by team members when needed) are all essential to the well being of patients. Subjective loading is part of the equation (i.e., social support, spirituality, emotional support, and Care Giver distress). As perceived by patient directly, subjective loading impacts the quality of life. Patients depend on relationships and attachments to help them through.

Supporting Quality of Life: Being supportive of the Care Giver and patient relationship has a positive impact on their coping style and distress. Increasing communication to get on the same page is beneficial (i.e., fear of choking to death must be addressed). Patient's needs change over time.

CLINICAL HIGHLIGHTS OF THE SYMPOSIUM – GIAN BORAZIO

AEOL 10150

Dr. Robert Miller, Forbes Norris Research Center, USA, reported on a potent antioxidant made by Aelous Pharmaceuticals that targets dangerous byproducts of cellular metabolism. This antioxidant was reported to be well tolerated by ALS patients. A larger trial is planned.

GA (Copaxone)

Some 30 patients participated in Dr. Paul Gordon's quest to find treatment in multiple sclerosis. Copaxone (a drug that may boost production of cells that suppress the immune system) was found to be safe and well tolerated in ALS patients. Further studies are planned.

TCH346

Dr. Robert Miller reported that TCH346 failed to yield benefits on the progression of ALS.

WEIGHT LOSS

Chio, Italy, reported that the rate of weight loss is more predictive than Body Mass Index (BMI).

SELF ADMINISTERED ALSFRS

Jackie Montes, USA, showed a poster about self administered ALSFRS. She also investigated palliative care and ALSFRS and found a paucity of information in hospice persons about ALS.

Equality of life and autonomy beginning to be investigated in Japan.

CAREGIVER SUPPORT

The average time a caregiver's help was required was 570 min/day, depending mostly on age and leg weakness. (Pioro) Although burden increases with cognitive change and bladder dysfunction, still 2/3 of caregivers find it rewarding and important caring for a loved one even when the burden is high.

COGNITION

Cognition may be affected with prefrontal cortex (a brain region) abnormalities in ALS patients (Strong, Canada). There is a strong correlation between cognitive impairment and tau protein seen in both astrocytes and neuron. Differences are found between molecular signatures in Alzheimer Disease (AD) versus ALS with different phosphorylation in the protein.

INCIDENCE AND PREVALENCE OF ALS CASES

Hardiman, Ireland, reported that incidence (newly diagnosed cases of ALS per year) and prevalence (number of people alive with ALS at a given time) of ALS is not clear outside Europe (6/100,000 vs 3 in USA). Lower risk of ALS has been shown in non smokers.

VENTILATION

Kim – Breath stacking (repeated deep breaths) with a bag is a simple way of over expansion of the lung. Ventilation education influences confidence of decision making.

ALLIED PROFESSIONALS MEETING

Lambert on Hope

Lambert said that inner locus of control or choosing one's attitude is the key to hope. For example, reframing the changes that occur in the body due to the disease put things into perspective. This might change the attitude. Discussion on hope and spiritual experience with patients might prove to be helpful.

“Life is delicate and we are all dying. Most of us are hopeful, it is normal to hope, regardless of circumstances.” Hall 1990

BASIC SCIENCE HIGHLIGHTS OF THE SYMPOSIUM

Further information on this segment is available on the Irish MDA website.

Crow et al (2005) - Manganese Porphyrin (a novel antioxidant) is actually a prooxidant which may be a conditioning stimulus that boosts up cell defenses and increases endogenous antioxidant activities. 250% increase in survival interval found in mouse models.

Heat shock response

ALS is characterized by motor neuron loss in the spinal cord, brainstem and motor cortex. In the SOD 1 mouse model, one can cause cell death by inducing a heat shock or treating cells with cyclosporine A and lactacystin. Giving a mild heat shock up-regulated Hsp27 in the mutant SOD

1 cells. The cells were then protected against subsequent more severe heat shocks. Over expression of hsp27 does rescue motor neuron loss.

Non –neural cells are important; degeneration is not cell autonomous. Microglia can be cytotoxic and may also be protective. Microglia is more active in SOD 1 mouse and can mediate balance between protection and toxicity. Abood, Forbes Norris Research Center, has proved that cb2 helps in SOD mouse.

Folding

Proteins are originally structured as a line of amino acids, similar to a chain. After the chain of amino acids is complete, the chain changes its structure and folds, spirals or takes on other shapes. This is helped by new connections made between different amino acids on the chain.) Misfolding of proteins may be important in ALS.

Chromosome 14q is an angiogenin (controlling blood vessels) and is a disease specific mutant that protects motor neurons. Activities are usually lost early and VEGF (vascular endothelial growth factor) helps protect this. Misfolded SOD in neurons with vacuolated mitochondria is common; small molecules may prevent misfolding. Aging has been shown to increase mitochondrial mutations.

Donoghue of Brown University spoke on deep brain stimuli in 30,000 people. Donoghue is looking to enter an era interfacing the brain with physical devices to assist patients with neuromuscular diseases. 100,000 patients worldwide are diagnosed with intact cognition and impaired motor functions; neural sensor will pick up and transmit the motor intention signal, and then decode signals from primary motor cortex (leg, arm face). The rate of spike firing is what contains the information. Microelectrode near a neuron tells the story. 100 microelectrodes in 4x4mm array will replace sensors. This serves as the brain gate by directing the neural controls of games, computers, and prosthetic devices.

Leigh Hochberg of Massachusetts General Hospital plans a pilot of this in 5 patients. How many neurons are in the motor cortex? Other neurons in frontal and parietal cortex might be important. It's important to give information about cortex changes at cellular level over time; also providing information on drug delivery vehicle, electrical stimulation vehicle, metric system to evaluate responses to therapy in cortex.

This device could also control wheelchair, computer, and other devices. This technology needs to become wireless and fully independent. For right now it is self contained and could also be used to reconnect bowel, bladder, vision, hearing functions.