ALSUntangled: Opening Up the X-Files of ALS

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The Original X-Files
- TV show, 1993-2002
- Movies
- Fox Mulder
  - Witnesses something strange
  - Disappearance of sister
    - Samantha; Aliens?
  - Spends the rest of his life
    trying to investigate/understand it and
    similarly bizarre happenings
  - Usually finds a rational
    explanation

Samantha
- 60 year old university professor, newly diagnosed with
  clinically definite sporadic ALS. She currently has minimal
  bulbar weakness, moderate arm and leg weakness. No
  obvious cognitive or behavior problems.

- Following education about the disease itself, she is presented
  with stage-appropriate, evidence-based management options
  including riluzole, multi-disciplinary team care
  - Neurology 2009;73:1218-1233

- She is also asked about participating in a research study

Samantha
- She opts for the first two, but declines the
  research study in favor of
  pursuing propofol

- Example of an
  alternative or off-label
  treatment (AOT, defined
  as non-mainstream
  therapy advertised to
  slow, stop or reverse ALS
  progression, without
  good evidence)
Common Decision?

- Survey of 350 patients with ALS
  - 50% responded
  - 54% admitted using at least 1 AOT
    - J Neurol Sci 2001;191:151-4

- Survey of 177 ALSRG clinicians
  - 23% responded
  - 50% stated they had patients using AOTs
    - ALS 2008;9:257-65

Why Try AOTs?

- ALS is a devastating, incurable, fatal disease with few proven treatment options
  - Neurology 2009;73:1118-1233
- Current treatments and those in foreseeable future may slightly slow progression
  - Lancet Neurol 2011;10:481-90
- 10% believe they will find a cure, 20% believe they will find something to make them better, 50% believe they will find something to slow progression
- "Peer pressure"
- "What further harm could come to me?"
  - J Neurol Sci 2001;191:151-4

Why Try AOTs?

- Many AOTs out there
  - Google search "ALS treatment" 35 million hits
- Proponents of AOTs make attractive claims
  - "Clinically Proven"
  - "Perfectly safe"

- [http://mototab.com/](http://mototab.com/)
Problematic?

- Information on AOTs ranges from absent to highly flawed to inaccurate

Ex. Absent Information

(Mototab website)

Clinical Research Study

The unique formulation of Mototab is a result of extensive study and research. Mototab is clinically proven to be a safe and effective treatment for Motor Neuron Disease. To download the summary of a clinical research study on the effectiveness of Mototab please click the link below.

Clinical Study soon to be posted here (Size: 96 Kb)

Requires Adobe Acrobat Reader.

Click here to download Adobe's Acrobat Reader.

-http://mototab.com/
Ex. Flawed Information

Details
- Investigators called patients and asked them to categorize themselves

Results from ALS treatment after 1 - 6 months (up to May 2008)

Placebo Effect

- Perceived improvement in health or behavior not attributable to a treatment, but rather a person's belief in the treatment
- Increased with:
  - Enthusiasm from treating provider
  - Expensive, invasive, complex treatments
  - Subjective outcome measures
  - Shorter intervals between treatment and outcome measures

http://skeptic.com/placebo.html

Ex. Inaccurate Information
“Reversible ALS” Does Exist


Ex. Inaccurate Information

Problematic?

- Documented Harms
  - Financial
  - Psychological
  - Physical
  - Scientific

-PLoS Med 2009; 6(2); e-pub 2009 Feb. 17
Scientific Harms of AOTs

- **Enrollment** in ALS trials is surprisingly low (<10%, or 2 patients/site/month)
- Pursuit of an AOT is a common reason patients decline enrollment

Consequences
- Trials take longer, are more expensive, may be terminated without a definitive conclusion
- Trial results may not be generalizable
- It will take longer than it should to find a cure for ALS

What To Do?

- Models for Decision Making in Doctor-Patient Relationship

<table>
<thead>
<tr>
<th>MD Role</th>
<th>MD Obligation</th>
<th>Patient Autonomy</th>
<th>Patient Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paternalism</td>
<td>Parent or guardian</td>
<td>Define and promote goals</td>
<td>None</td>
</tr>
<tr>
<td>Autonomy</td>
<td>Assent</td>
<td>Assist with procurement</td>
<td>Central and absolute</td>
</tr>
<tr>
<td>Consumerism</td>
<td>Technical expert</td>
<td>Provide relevant factual info</td>
<td>Central and absolute</td>
</tr>
<tr>
<td>Shared decision-making</td>
<td>Advisor</td>
<td>Provide info and opinion</td>
<td>Respected</td>
</tr>
</tbody>
</table>

Paternalism

**Strengths**
- Physicians have many years of specialized training, experience, tools to critically evaluate treatment options according to efficacy and side effects
- Lasted a long time so there must be something about it that satisfies needs of both parties

**Weaknesses**
- Patient may not share same goals, values, acceptable benefits and risks
- Patients may want more or less than the physician is willing to give at particular time (active seekers, selective seekers, information avoiders)
- Can be abused, at bedside and in clinical “research”
Autonomy

Strengths
• Respect for patient-defined values and goals is and should be paramount
• Allows patients to proceed with information gathering at their own pace (active seekers, selective seekers, information avoiders)

Weaknesses
• Underutilization of physician education, training and experience
• Patient values and goals may not be well-defined or stable over time
• Information patient is using may be flawed

“In Between” Models

Strengths
• Utilize physician talents and skills while still allowing patient to ultimately define values, goals, acceptable risks and benefits

Weaknesses
• In consumerism, the physician is reduced to a detached information source; patient values may be uncertain and may change
• Fine line between shared decision-making and paternalism
• Take more time

What To Do?

• Most patients (and doctors) prefer shared decision-making
  — Patient Education and Counseling 2007;65:189-196
  — BMD Family Practice 2007;8:4
• Shared decision-making is associated with improved compliance and health outcomes
  — Med Care 1989;37:110-127
  — Med Care 1991;29:1167
  — BMJ 2001;323:908-911
  — J Gen Intern Med 2002;17:243-252
  — J Gen Intern Med 2002;17:857-866

• But time in medicine is becoming more scarce...
Shared Decision-Making

- Van den Berg
  - Systematically Investigated Beijing West Hill Hospital and Rehabilitation Center (OEC’s injected into brains of PALS)
    - Critiqued theory, “published data” claiming “safe” and “50-70% improved”
    - Visited clinic, interviewed physicians
    - Followed 7 PALS with validated ALS outcomes
  - Reported findings, advised against going
    - Very brief subjective benefit in 2 PALS
    - No objective evidence benefit
    - Documented harms (blood clot, respiratory failure & death)
    - $25,000

ALSUntangled

- Started 2009 as ALSRG project
- Goal: develop group of clinicians/scientists that systematically assess AOTs, toward ultimately helping patients with ALS make more informed decisions
- Methods
  - Inputs from PALS
  - Investigations/Reviews
  - Outputs

Inputs

- Make it simple for PALS all over the world to access ALSUntangled with queries
  - Face to face meetings in clinics
  - Email: bedla001@mc.duke.edu
  - Twitter: twitter.com/#!/alsuntangled
    - Don’t need to remember specific email address, just key word
    - Everyone can see what is being asked about
  - Website www.alsuntangled.org
    - Describes program, email address, how to use Twitter
Twitter Activity

FOLLOWERS
3/10: 137
3/11: 363
3/12: 643
4/13: 1,020
7/13: 1,144

TWEETS
3/10: monthly;
3/11: weekly
3/12: daily

OPEN QUERIES
3/10: 26
3/11: 31
3/12: 40
4/13: 64
7/13: 85

Reviews

- Team
  - Originally: 38 members, 4 countries
  - Today: 85 members, 10 countries
    (USA, Canada, Ireland, Israel, Spain, Thailand, Sweden, Poland, France, Russia)

- Platform for Interaction
  - Email list serve (more than 100 emails in past year)
Reviews

- **SOP**
  - Multiple attempts to contact proponents
  - Materials from clinic (e.g., Website)
  - PubMed Search (relevant publications)
  - Google Search (news, blogs)
  - Poll ALS Untangled Team (cases with objective measures)
  - Patients Like Me review (cases with subjective measures)
  - Visit Clinic
    - Review infrastructure
    - Interview proponents
    - Review records, interview “best successes”

Reviews

- Systematic Investigation Form
  - Clinic Name:
  - Location(s):
  - Advertising:
  - Name of Treatment Offered
  - Diseases Treated Besides ALS:
  - Detailed Description of Treatment:
  - Cost:
    - Amount Billed Each Visit:
    - Number of Visits Required:
    - Amount Paid by Insurance Companies/Agency:
  - Theoretical Benefits/Rationale:
  - Theoretical Risks:
  - Actual evidence of benefit (and type of evidence)
  - Actual List of AEs Encountered in Patients with ALS
  - Consent Process:
    - Inclusion/Exclusion Entry Criteria
    -Outcome Measures Followed:
    - Efficacy:
    - Safety:
  - Facility Description:
  - Critique/Commentary:

Outputs

- Reports published “free open access” in journal Amyotrophic Lateral Sclerosis
- Group authorship
  - Members get minimum 48h to comment on draft
  - “Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.”
- 1000 words
- Standard format
  - What is the therapy being investigated?
  - Where did the idea for the investigation come from?
  - What is the rationale for using this therapy in PALS?
  - How is it obtained and delivered to PALS?
  - What are the efficacy data for this therapy in ALS?
  - What are the safety data for this therapy in ALS and in other relevant diseases?
  - How much does it cost?
  - Based upon the above, what are our recommendations?
Lessons Learned

- **It is rarely possible to know the motivation of the AOT proponent**

- Larry Stowe (Stowe/Morales Protocol)
  - Impersonated physician
  - Lied about relationships with American Universities and Agencies such as FDA
  - Made impossible claims on hidden camera, later denied them
  - Currently arrested, awaiting trial
    - ALS 2010.11.414-416
Welcome to mototab.com!

Meet probably you are here in search of a treatment for Motor Neuron Disease. Rest assured that your search is now over! Mototab is the world's most relied upon and clinically proven natural treatment for Motor Neuron Disease.

For more information on our fully guaranteed treatment, Mototab, please click here.

To view information on Motor Neuron Disease please click here.

Clinical Research on Mototab
Mototab is clinically proven to treat Motor Neuron Disease successfully. You may download a summary of our clinical study in Adobe's PDF format. Click here for details.

Mototab Guarantee
Mototab is a completely guaranteed treatment. You are at no risk for trying Mototab. Click here for details.

Peritab, S yrotab, Os tetotab
Amylotab, MD-Tab...

http://mototab.com/
Lessons Learned

• **AOT proponents do some things really well**
  – I watched Dr. Hickey interact with his patients and then I interviewed them separately
  – Qualities he demonstrated that his patients said they did not find in their mainstream ALS doctors
    • Optimism
    • Respect
    • Responsiveness

Lessons Learned

• **The most obviously flawed/bogus clinics/AOTs share things in common**
  – Advertised as “dramatically effective” or “cure all” for multiple diseases with different pathophysiology
  – Advertised as “perfectly safe”
  – Non-MD making medical recommendations
  – Lack of oversight/consent
  – Lack of standardized protocol
  – Large up front out of pocket cost
  – Subjective or no outcome measures
  – Lack of follow up

Lessons Learned

• **Some AOTs warrant further study**
  – Plausible mechanism
  – Multiple subjective reports suggesting similar benefit, or objective data
  – Some data available on safety and cost

• **Patient reports should be considered a valid model for treatment candidate ideas**
  – Viagra
  – Nuedexta
Aimspro

- Hyperimmune goat serum injected subcutaneously
- Modulates inflammation
- Single autobiographical case report, limited info on diagnosis
- Author performed his own PFTs, combined MEP, MIP, SNIP, FVC into one measure RFT
- Increasing dosages (intervals) appeared to result in improving, eventually reversing RFT decline; no effect on muscle strength
  - Bias, lack of validation of outcome, other therapies also used
- “No side effects,” £19,000 per year
- Further studies underway:

Coconut Oil

- Background

- Rationale(s) for Use in ALS
  - Converted into ketone bodies which may ameliorate energy production problems secondary to mitochondrial dysfunction
  - Source of fat calories, raises cholesterol
Coconut Oil

• Data
  – Animal (SOD1-G93A mice)
    • No trials of coconut oil
    • Ketogenic diet
      – Significantly better preserved rotarod function and motor neuron counts
    • High fat diet
      – Significantly higher BMI, preserved motor neuron counts, improved survival

Fecal Transplants (FT)

Rationale

• Some diseases (ex. Crohn’s) are caused by alteration in gut bacterial composition (a.k.a. “microbiome”)
• These can improve with FT which re-establish a more normal microbiome
• This is a hypothesized cause of some cases of ALS (Longstreth 2005)
  – Some bacteria (ex. clostridial species) produce toxins that can affect both central and peripheral motor neurons
  – Constipation is common in ALS and may have many causes including altered microbiome

Fecal Transplants (FT)

Data

• No animal or human studies on microbiome in ALS, no animal or human trials of FT
• A physician in Australia performed FT on a patient with ALS (for chronic constipation) and reported that they “got out of their wheelchair and were able to dance” with their wife, though later declined
• Case reports of FT helping patients with PD, MS, autism, dystonia, AD, MG

Risks and Costs

• Risks include infection, injury from insertion of tubes
• Costs range from $800 (screening, supplies, 10 treatments at home) to $4000 (at a FT clinic)
ALS Untangled Challenges

- Widening gap between open and completed investigations
  - Rapid increase in twitter followers, requests
  - Lack of available information on some topics
  - Difficulty finding lead authors
  - Hard limit on number of ALS journal issues each year
- Limited opportunities for comments/rebuttals related to published investigations
- Difficult to measure “usefulness”
- No resources for follow up study of interesting AOTs

Opportunities, Next Steps

- Creating incentives for lead authors (meeting expenses)
- Publishing “early online” on ALS journal website
- Expanding our website to allow comments/rebuttals via twitter
- Allowing clients to vote for the open reviews they most want to see
Is ALSUntangled Useful?

Top 50 Most Viewed Articles in Amyotrophic Lateral Sclerosis 2012

- Source: ALS Editorial Board Meeting 2012

ALSUntangled: Conclusions

- Investigation of AOTs is timely and important
- “The Truth Is Out There” but it isn’t always easy to find
- ALSUntangled uses social networking to bring patients and clinician/scientists together to systematically review and report on AOTs
- Interesting lessons being learned (including ideas for future studies)
- Challenges are being addressed by incentivizing new authors, modifying website
- ALSUntangled reviews are being downloaded frequently

Where Does ALSUntangled Fit?

- Broad Goal: Cure ALS
- Why No Cure?
  - We don’t know what causes most cases
  - We don’t understand disease progression
  - It takes a long time to make a diagnosis
  - Our measurement tools are noisy and slow to change
  - It is a rare disease with limited resources available for study
- Enrollment in ALS research studies is surprisingly low
  - My focus
  - Working with ALSRF, NEALS, WALS, Packard
Raise Awareness of Research Options

- Advertising via National ALS Registry
- Speaking to patient groups, writing in patient-centric literature
- Training research advocates (including patients and caregivers)

ALS Clinical Research Learning Institutes

- Modeled after successful programs in PD, cancer
- Lectures on research including ethics, informed consent, trial designs, statistics
- Lectures on advocacy including tips on public speaking, writing letters to the editor, writing letters to congress, internet tools, meeting with the press and congress
- Discussion and debate between faculty and attendees regarding research barriers and how to address them; both leave with new appreciation for the others’ issues

Outreach Efforts by NEALS Research Ambassadors

<table>
<thead>
<tr>
<th>Activity</th>
<th>Number of Each</th>
</tr>
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<tbody>
<tr>
<td>Speaking at a Fundraiser</td>
<td>11</td>
</tr>
<tr>
<td>Speaking at a Support Group</td>
<td>6</td>
</tr>
<tr>
<td>Speaking to a Congressman</td>
<td>7</td>
</tr>
<tr>
<td>Interview</td>
<td>7</td>
</tr>
<tr>
<td>Writing in a Newspaper</td>
<td>17</td>
</tr>
<tr>
<td>Writing in a Blog</td>
<td>7</td>
</tr>
<tr>
<td>Writing in a Website</td>
<td>40</td>
</tr>
<tr>
<td>Writing to a Congressman</td>
<td>14</td>
</tr>
</tbody>
</table>

This table shows the types of outreach efforts being undertaken by our NEALS Research Ambassadors. Through these, they are educating and advocating about ALS research to patients, clinicians, press and policymakers. We are very proud of them! If you would like to be a NEALS Research Ambassador please apply for the 2013 ALS Clinical Research Learning Institute here.
Reduce Travel Burden

- Build more clinics
  - Clinic Mapping (ex. ALSA)
- Expand number of clinics with research studies
  - Consortia (ex. NEALS at 102 sites)
- Develop home based outcome measures
  - Ex. Arimoclomol trial for patients with FALS1 is underway using home spirometry, telephone ALSFRS-R scores

Optimize Study Presentations

- *Physicians* should present research option (not ancillary staff)
- Address misconceptions, AOTs
- Include video (ex. NEALS Ceftriaxone Study)
  - This approach improved patient knowledge and enrollment in cancer studies
  - *J Thorac Oncol 2008;3:3-5*

Samantha: One Resolution

- Patient given a copy of ALSUntangled 22: Propofol (in press)
  - Propofol is a very short acting amnestic/hypnotic agent that is primarily used for procedural sedation, or to induce or maintain general anesthesia
  - Mechanisms that might be useful in ALS: blocks sodium channels and promotes inhibitory (GABA-ergic) activity, modulates oxidative stress, inflammation and endocannabinoid system
  - BUT propofol has a very short half life, and thus it is unlikely that a single infusion could effect these mechanisms long enough to help a neurodegenerative disease such as ALS
Samantha: One Resolution

- On ALS.net, 6 users reported improvements in ALS in either themselves or their spouse following exposure to propofol
  - Drug was given with other drugs and procedures at wide range of doses
  - Improvements described include limb strength, dexterity, walking, breathing, speech, and swallowing; these started within a few days of propofol exposure, and lasted between 9 days and 1 month
- Records were requested on all these patients, but received for only 1; records confirm that the user has ALS, and was exposed to 100mg propofol for septoplasty on 5/14/13

Samantha: One Resolution

- In a survey of ALSUnangled investigators, 213 patients from 3 ALS centers received propofol during PEG placement. No improvements were noted in any of these patients by either the surgery teams or their neurologists.
- Within the PRO-ACT database 14 patients with confirmed ALS were exposed to propofol at various dosages. ALSFRS-R scores before and after propofol exposure are available for 10 of these. None of these patients showed a significant improvement in their ALSFRS-R scores with propofol.

Samantha: One Resolution

- Propofol has many serious risks including respiratory depression, cardiac arrhythmias such as bradycardia and asystole, hypotension, metabolic acidosis, rhabdomyolysis, renal failure and death
- Due to its significant risks, many different national societies of anaesthesiology have stated that propofol should be given only by those trained in administering general anaesthesia and with appropriate cardiopulmonary monitoring
- While the cost of the drug itself is not high, the cost of administration with appropriate monitoring is likely to be more than a thousand dollars per treatment
Samantha: One Resolution

- While we cannot conclusively rule out a very brief benefit from propofol in rare patients with ALS, the risks and costs involved do not appear to justify its use. **We strongly discourage the off label use of propofol in ALS patients at this time.**

Samantha: One Resolution

- Patient educated on option of participation in research studies, including clearing up misconceptions
- Decides to forgo propofol in favor of participation in new ALS clinical trial
- Attends ALS Clinical Research Learning Institute; becomes advocate for ALS Research

Thanks

- Patients
- MND
- ALSRG
- ALSA
- MDA
- WFNALS
- ALS journal
- 60 Minutes
- Quackwatch
- Patients Like Me
- ALS Worldwide
- ISSOR