Untangling the ALS X-Files

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Duke ALS Clinic

Attendees are advised that portions of this webinar will be recorded for later viewing in our archives. If you would like to review the recording, please refer to our website, for information (www.alsa.org).

Hosted by:
The ALS Association
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Untangling the ALS X-Files

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The Original X-Files

• TV show, 1993-2002; 2016; Movies
• Fox Mulder
  • Baby sister Samantha disappeared
    • Aliens?
  • Spends the rest of his life trying to prove that aliens and other supernatural creatures are real
• Each episode would open with a strange occurrence
  • Usually a rational explanation

http://en.wikipedia.org/wiki/The_X-Files
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 Dean Kraft’s Energy Healing
Definition

• Alternative or Off Label Therapy (AOT)-treatment advertised to slow, stop or reverse ALS without good scientific evidence
How Often and Why?

• At least 50% of PALS try AOTs
  - J Neurol Sci 2001;191:151-4
  - ALS 2008;9:257-65

• Current ALS treatments and those in foreseeable future may improve quality of life, slightly slow progression
  - Neurology 2009;73:1218-1233
  - 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
  - J Neurol Sci 2001;191:151-4
AOTs on the Internet

- Many being advertised
  - Google search “ALS treatment” >50 million hits

- Proponents make attractive claims
  - “World’s most relied upon”
  - “Clinically proven”
  - “Guaranteed”

http://mototab.com/
AOTs on the Internet

- Anecdotes are the most common type of information used to support efficacy claims

"After reviewing [Patient 202]'s past medical history, it is in [both treating doctors'] opinion that the patient has greatly benefited from GM604 over the past six weeks when the drug was administered three times a week. During our initial assessment, the patient had rapid tongue fasciculation which developed over July and August but decreased dramatically with the medication. The patient has stopped biting her tongue, which were also reflected in her previous medical records. This is a reversal and an unexpected benefit from the medication. Moreover, the patient's limb progression has completely plateaued."

http://www.genervon.com/genervon/PR20151210.php
Potential Flaws in Anecdotes

• We don’t know who this person is or how their diagnosis was confirmed
  • At least 1 example of a company having “made up” anecdotes to sell their treatments

Patient stories on the web may not be real

LISA GUALTIERI, PHD | PATIENT | APRIL 13, 2010

“On the Internet, nobody knows you’re a dog” was the caption of the famous cartoon by Peter Steiner in the July 5, 1993 issue of The New Yorker. The same is true of patient stories on health Web sites: nobody knows who really wrote them.

In the case of Lifestyle Lift, the company agreed to pay a $300,000 settlement last year to New York State because their patient stories were employee-generated.

http://www.kevinmd.com/blog/2010/04/patient-stories-web-real.html#more-43464
Potential Flaws in Anecdotes

- Outcome measures of uncertain clinical significance reported
- Fasciculations not usually bothersome
- Fasciculation frequency not correlated with limb strength or disease progression
Potential Flaws in Anecdotes

- Failure to account for the natural history of the disease
  - It is not uncommon for PALS to have periods of stability (plateaus) or small improvements (small reversals)
  - 75% of participants in PRO-ACT had a plateau lasting 6 weeks at some point in their illness

  - Neurology. 2016 Mar 1;86(9):808-12

On Placebo

6 weeks
Failure to Recognize Flaws

• Common

• Why? Evolution

“we have evolved brains that pay attention to anecdotes because false positives (believing there is a connection between A and B when there is not) are usually harmless, whereas false negatives (believing there is no connection between A and B when there is) may take you out of the gene pool.”

http://www.scientificamerican.com/article/how-anecdotal-evidence-can-undermine-scientific-results/
Underappreciated Harms from AOTs

• Financial
  • Ex. ALS 2010;11:414-416

• Physical
  • Infections, blood clots, tumors, deaths
  • Ex. ALS 2010;11:328-330

• Scientific
  • Low enrollment rate (2 patients/site/month) in our trials
    • ALS 2008;9:257-65
Why Are Harmful Anecdotes Less Influential?

• “I already have ALS, what worse could possibly happen?”

• Anecdotes describing harm are not as easy for PALS to find
  • Reporting bias
  • Not on proponents’ websites
  • Scattered across many different Internet locations (ex. different chat rooms)

• Scientific literature
  • Difficult to access ($$)
ALSUntangled

• Started 2009
• Goal: develop group of clinicians & scientists that systematically assess AOTs, toward ultimately helping PALS make more informed decisions

• Methods
  • Inputs
  • Investigations/Reviews
  • Outputs
Inputs from PALS, CALS

- Face to face visits or emails with one of our team members
- Twitter
  - Don’t need to remember specific email address, just key word
  - Currently have more than 3000 Twitter followers
  - More than 250 AOTs that we have been asked to review
Reviews

• Team
  • >100 members, 10 countries (USA, Canada, Ireland, Israel, Spain, Thailand, Sweden, Poland, France, Russia)

• Standard operating procedures (SOPs) guide everything we do, from information gathering to writing, crowd-sourcing drafts
# ALSUntangled Table Of Evidence (TOE)

<table>
<thead>
<tr>
<th>Evidence category</th>
<th>U</th>
<th>F</th>
<th>D</th>
<th>C</th>
<th>B</th>
<th>A</th>
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</thead>
<tbody>
<tr>
<td>Mechanistic plausibility</td>
<td>Unknown</td>
<td>Implausible; would violate known principles or laws of biology</td>
<td>Acts on a biological mechanism but it is not clear than this mechanism is relevant in ALS</td>
<td>Theoretically and plausibly acts on an ALS-relevant mechanism in humans</td>
<td>Shown in a peer-reviewed publication to act on a relevant mechanism in pre-clinical model(s)</td>
<td>Shown in a peer-reviewed publication to act on a relevant mechanism in humans</td>
</tr>
<tr>
<td>Pre-clinical models (animal or cell models recognized by ALSUntangled reviewers to be relevant to ALS)</td>
<td>None</td>
<td>The only studies available show no benefit</td>
<td>One or more non-peer reviewed studies reporting benefits (published on a website or in an abstract)</td>
<td>One or more peer-reviewed publication(s) reporting benefits in flawed studies (*)</td>
<td>One peer-reviewed publication reporting benefits in a well-designed study (*)</td>
<td>Two or more peer-reviewed publications reporting benefits in well-designed studies (*)</td>
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<td>Patient case reports</td>
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<td>Risks (harm that occurred on this treatment)</td>
<td>Unknown</td>
<td>At least 5% of exposed patients experienced death or hospitalization</td>
<td>More than 0% but less than 5% of exposed patients experienced death or hospitalizations</td>
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Can help PALS validate, centralize both positive and negative anecdotes, temper conclusions based on natural history of disease
Reviews published in ALS-FTD and on our website.

All free Open Access

39 published reviews (each took around 40 hours to complete)

Top 9 most read articles in ALS-FTD
-More than 90K downloads
Lessons Learned—Proponents

• Some are snake oil salesmen
  • ALS 2010;11:414-416
  • [http://timesofsandiego.com/crime/2014/05/05/la-mesas-21st-century-snake-oil-salesman-on-60-minutes-gets-6-year-term/](http://timesofsandiego.com/crime/2014/05/05/la-mesas-21st-century-snake-oil-salesman-on-60-minutes-gets-6-year-term/)

• More are “true believers”

• Many have mannerisms that mainstream doctors should adapt
  • Optimism, respect, responsiveness
    • ALS2009;10:490-491

Dr. Joe Hickey—A True Believer
Lessons Learned-AOTS

• Many are bogus
• Some have plausible mechanisms
  • Alter patterns of gene expression (Lunasin, Protandim)
  • Anti-oxidant, anti-inflammatory (Cannabis, MitoQ, Lutimax, Inosine, HBOT)
  • Toxin modulators (Fecal Transplants, L-Serine)
Nelda Buss’ Dramatic ALS Reversal Is Real!

- Gradual, painless, limb onset weakness at age 43
- Within 6m, unable to walk or accomplish ADLs
- Within 12m, quadriplegic and short of breath
- No relevant PMH, FH, SH
- Seen at UVa (Wooten, Pascuzzi, Phillips)
  - Exams showed diffuse arm and leg weakness, pathologically brisk jaw, limb reflexes, normal mental status, cranial nerves, sensation
  - 2 sets of NCS showed no sensory neuropathy or motor conduction block
  - 2 EMGs showed progressive denervation and reinnervation cervical, reinnervation lumbar segments
  - Cervical myelogram unremarkable
  - Blood (ESR, RPR, TSH) and CSF unremarkable
  - Diagnosis: ALS

- Stopped seeing doctors after Dean Kraft, but multiple videos show near complete recovery of arm and leg strength (max recovery 2y post nadir)

29 Other Examples of Dramatic ALS Reversals

- Validated ALS diagnoses, dramatic improvement in at least 1 recognized objective ALS outcome measure
- What happened to these people is so different from the natural history of ALS that it warrants further study

- 1 in ALS 2016; Epub ahead of print
- 1 in ALS 2016;17:154-156
- 1 in Ann Neurol 2014;75:363–373
- 1 in Muscle & Nerve 2014;49:455-457
- 1 in ALS 2014;15:622-626
- 1 in J Clin Neurosci 2006;13:1033–1036
- 1 in Rinsho Sinkeigaku 2000;40:1090– 5
- 1 in Eur Neurol 1993;33: 387 – 9
- 7 in Neurology 1991;41:1541 – 4
- 2 from my own clinic
- 12 others sent me records
Unexpected and Dramatic Improvements as a Model for Drug Discovery

- In ALS
- Nuedexta

**Clinical research**

*The role of serendipity in drug discovery*

Thomas A. Ban, MD, FRCP(C)

**Definition of serendipity**

Serendipity is one of the many factors that may contribute to drug discovery. It has played a role in the discovery of prototype psychotropic drugs that led to modern pharmacological treatment in Psychiatry. The idea of a drug discovery project being guided by chance, luck, or fortunate circumstances has been recognized and emphasized by many researchers and clinicians in the past. However, the discovery was serendipitous because an error in a test led to an unexpected result, and in the case of the discovery of the sedative drug, the error led to the discovery of a new drug.

**Author:** Thomas A. Ban, MD, FRCP(C)

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**Neur Ther 2014;17:15**
Replication of ALS Reversals (R.O.A.R.)

• Small pilot trials of AOTs associated with Dramatic ALS Reversals
  • Because most of AOTs are “GRAS” (generally regarded as safe), and because this program is looking for the largest signal ever in an ALS trial (reversal), these can have:
    • Wide inclusion criteria
    • Lack of placebo control (historical controls)
    • Few in person visits (virtual visits)
    • Results available in real time (PatientsLikeMe)
    • Protocols published (www.alsreversals.org)

• First R.O.A.R. Trial (Lunasin) enrolled at a record pace, interim results at https://f1000research.com/posters/5-2916
Other Explanations for Dramatic ALS Reversals

• Under-recognized ALS mimic?

• Potentially fluctuating, antibody-mediated ALS mimics in the literature
  • Atypical celiac disease
    • Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2016;17:307-309
  • Multi-focal motor neuropathy with upper motor neuron signs
    • Bedlack RS, Torres S, Pastula D. IVIG-Responsive Upper and Lower Motor Neuron Disease with NP-9 Antibodies, Persisting Long After Infliximab Therapy; in Companion to Peripheral Neuropathy, Illustrated Case Reports Plus. Elsevier (New York) 2010
  • Myasthenia gravis with upper motor neuron signs
    • Adv Biomed Res. 2015 Feb 23;4:58
Other Explanations for Dramatic ALS Reversals

• Endogenous mechanism for “beating” ALS?

• Precedent: HIV elite controllers
  • 1% of those infected with HIV
  • Most have mutation called CCR5-Δ32 that impairs viral entry
  • Maraviroc (Pfizer) first FDA approved CCR5 antagonist

http://en.wikipedia.org/wiki/CCR5_receptor_antagonist#Drug_development
Study of ALS Reversals (St.A.R.)

• Find more Dramatic ALS Reversals
  • Advertising on traditional and social media
  • Getting records to confirm diagnosis and dramatic, improvement in objective measurement

• Enter them all into the same database
  • Compare demographics, disease characteristics, co-morbidities to PRO-ACT and National Registry participants

• Get blood samples on as many as we can
  • Antibody profiles
  • Genetics

Dan Harrison MSIII
Study of ALS Reversals (St.A.R.)

• Compared to controls, ALS reversals were younger, more often male, more likely to be black and more likely to have limb onset.

• PRO-ACT does not contain information on the co-morbidities of its participants, as patients with co-morbidities are often excluded from clinical trials. However, the prevalence of myasthenia gravis in our cases (8%, n=2) was higher than estimates of prevalence in the general population (0.008%).
Study of ALS Reversals (St.A.R.)

- There were 126 independent medications and supplements used by cases during the time of their ALS reversal including 21 AOTs used by more than one reversal. The odds of a reversal were significantly greater for participants exposed to 6 of these AOTs when compared to unexposed participants after Bonferroni correction (p<.0004).

<table>
<thead>
<tr>
<th>AOT</th>
<th>OR</th>
<th>CI</th>
<th>Statistical Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luteolin</td>
<td>450</td>
<td>59.9-3,380</td>
<td>( \chi^2 = 35.3 )</td>
<td>p&lt;.0001</td>
</tr>
<tr>
<td>Curcumin</td>
<td>300</td>
<td>47.1-1910</td>
<td>( \chi^2 = 36.5 )</td>
<td>p&lt;.0001</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>150</td>
<td>28.2-796</td>
<td>( \chi^2 = 34.6 )</td>
<td>p&lt;.0001</td>
</tr>
<tr>
<td>Copper</td>
<td>32.1</td>
<td>7.07-145</td>
<td>( \chi^2 = 20.2 )</td>
<td>p&lt;.0001</td>
</tr>
<tr>
<td>Glutathione</td>
<td>24.2</td>
<td>5.40-108</td>
<td>( \chi^2 = 17.3 )</td>
<td>p&lt;.0001</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>6.74</td>
<td>2.42-18.8</td>
<td>( \chi^2 = 13.3 )</td>
<td>p=.0003</td>
</tr>
</tbody>
</table>
Conclusions

• There is no such thing as a weird human being, It's just that some people require more understanding than others. ~ *Tom Robbins*
Conclusions

• When it comes to AOTs, “The Truth Is Out There” but it isn’t always easy to find
  • Anecdotal data is especially problematic in ALS, commonly misinterpreted

• ALSUntangled uses social networking to bring PALS, clinicians & scientists together to systematically review and report on AOTs
  • Can help validate, centralize both positive and negative anecdotes, temper conclusions based on natural history of disease
Conclusions

• Proponents of AOTs have mannerisms that mainstream doctors can learn from
  • Optimism, respect, responsiveness

• Some ALS anecdotes clearly warrant further attention
  • Dramatic ALS Reversals
    • R.O.A.R. (pilot trials of agents associated with dramatic ALS reversal)
    • St.A.R. (search for under-recognized mimics, endogenous mechanisms for beating the disease)
Thanks

• PALS
• ALSA and all of our other funding sources
• PatientsLikeMe, Neurobank, Origent, ALSUntangled reviewers
• Duke ALS Care Team