

Welcome!

April 17, 2017

2:30 pm ET/11:30 am PT



Untangling the ALS X-Files

Rick Bedlack, MD, PhD
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
National Office-Care Services

Untangling the ALS X-Files

Richard Bedlack MD PhD

Duke ALS Clinic

Durham NC, USA

Disclosures:

Research support from ALSA,
MNDA, Cytokinetics,
Neuraltus, GSK;
Consulting support from ALSA,
Avanir, Cytokinetics, Neuraltus,
Ultragenyx



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

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

Dean Kraft - Energy Healer

www.deankrafthealer.com

[Plain Text Version](#)



Dean and Rochelle Kraft

REPOSITORY OF MEDICAL REPORTS AND SCIENTIFIC RESEARCH
OF THE MOST DOCUMENTED HEALER OF OUR TIME

NEW TELEPHONE NUMBER

Dean and Rochelle Kraft, 527 Third Ave., Suite #266, New York, NY 10016 Phone 212-501-2222

"THE MIND/BODY CONNECTION"

[Home](#) [Patient Testimonials](#) [Physician Testimonials](#) [Case Histories](#) [Research](#) [Television & Radio](#) [Published Articles](#) [Books](#) [Lectures & Seminars](#) [Map](#)



Definition

- Alternative or Off Label Therapy (AOT)- treatment advertised to slow, stop or reverse ALS without good scientific evidence

Dean Kraft - Energy Healer

www.deankrafthealer.com

[Plain Text Version](#)



Dean and Rochelle Kraft

REPOSITORY OF MEDICAL REPORTS AND SCIENTIFIC RESEARCH
OF THE MOST DOCUMENTED HEALER OF OUR TIME

NEW TELEPHONE NUMBER
Dean and Rochelle Kraft, 527 Third Ave., Suite #266, New York, NY 10016 Phone 212-501-2222

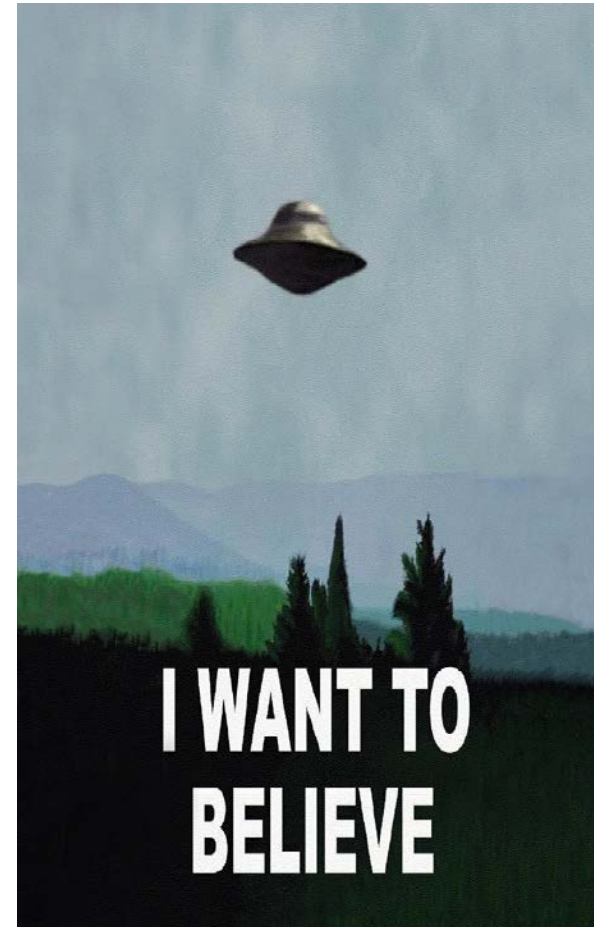
"THE MIND/BODY CONNECTION"

[Home](#) [Patient Testimonials](#) [Physician Testimonials](#) [Case Histories](#) [Research](#) [Television & Radio](#) [Published Articles](#) [Books](#) [Lectures & Seminars](#) [Map](#)



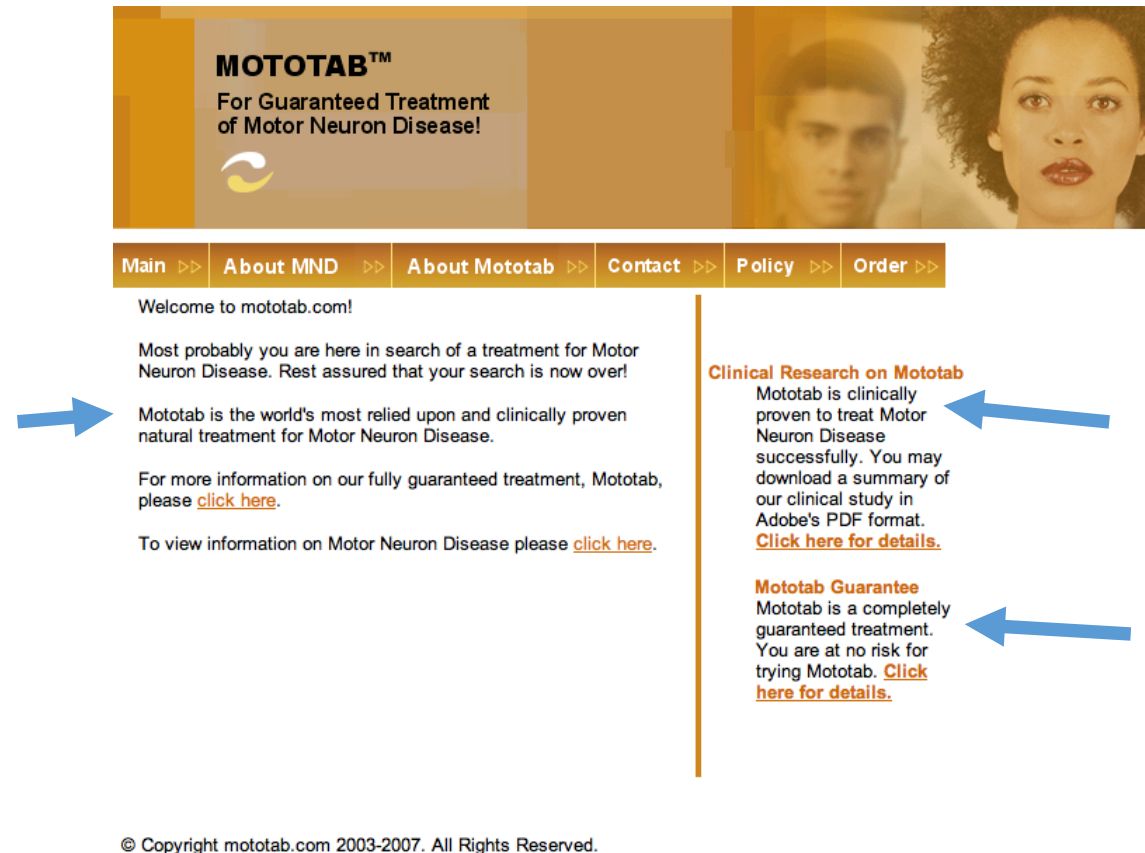
How Often and Why?

- 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”



MOTOTAB™
For Guaranteed Treatment of Motor Neuron Disease!

Main >> About MND >> About Mototab >> Contact >> Policy >> Order >>

Welcome to mototab.com!

Most 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.](#)

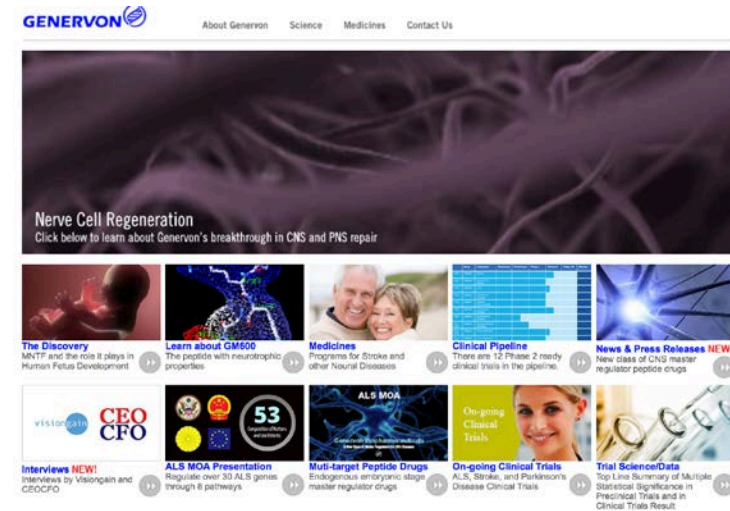
Mototab Guarantee
Mototab is a completely guaranteed treatment. You are at no risk for trying Mototab. [Click here for details.](#)

© Copyright mototab.com 2003-2007. All Rights Reserved.

The screenshot shows the Mototab website with a header banner featuring a man and a woman. Below the banner is a navigation menu with links: Main >>, About MND >>, About Mototab >>, Contact >>, Policy >>, and Order >>. The main content area contains a welcome message, a statement about the search for a treatment, a claim that Mototab is the world's most relied upon and clinically proven natural treatment, and two links to click here. On the right side, there are two sections: 'Clinical Research on Mototab' and 'Mototab Guarantee', both with links to click here for details. Blue arrows point from the text in the list to these specific sections on the website.

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


Strength, physical activity, and fasciculations in patients with ALS


Farrah J. Mateen , Eric J. Sorenson & Jasper R. Daube

Pages 120-121 | Received 13 Jul 2007, Accepted 23 Dec 2007, Published online: 10 Jul 2009

 Download citation  <http://dx.doi.org/10.1080/17482960701855864>

 Full Article

 Figures & data

 References

 Citations

 Metrics

 Reprints & Permissions

 Get access

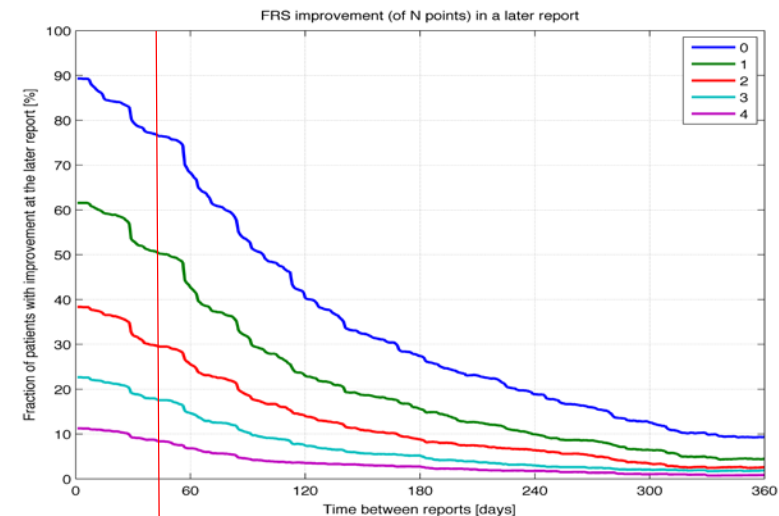
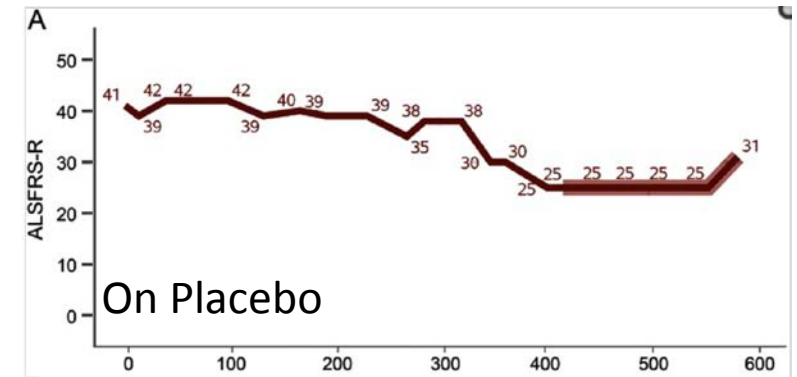
Abstract

Fasciculations are a nearly universal feature in people with amyotrophic lateral sclerosis (ALS). The prognostic value of fasciculations remains uncertain. Twenty-four patients with ALS were evaluated for the effects of atrophy, limb weakness, disease duration, and physical activity on fasciculation frequency (as measured by surface electromyography and clinical counting). Variables were compared by multiple linear regression. As strength of the limb deteriorated, the number of fasciculations in the same limb increased, as long as physical activity was maintained or increased. Fasciculation frequency was not associated with the duration of ALS ($r = 0.22$; $p = 0.30$) and was independent of the degree of limb weakness ($p > 0.05$) and limb atrophy ($p > 0.05$). No prediction of disease duration could be made based on fasciculation frequency alone. Fasciculations therefore appear to have diagnostic, but not prognostic, utility in the care of people with ALS.

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

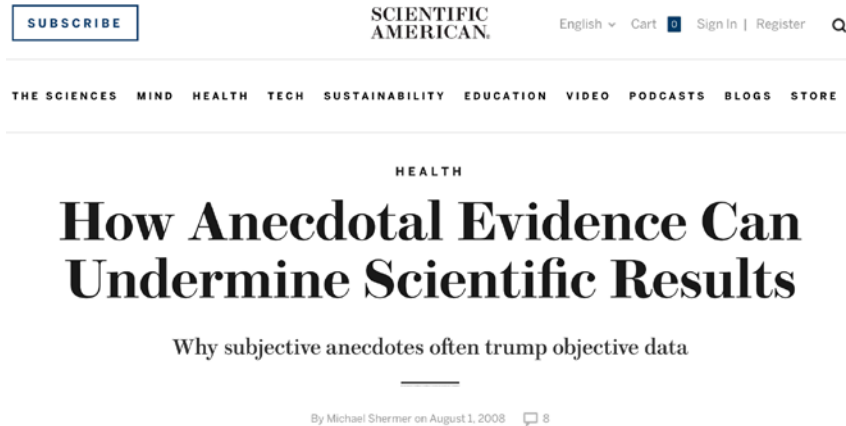
• *Neurology*. 2016 Mar 1;86(9):808-12



6 weeks

Failure to Recognize Flaws

- Common



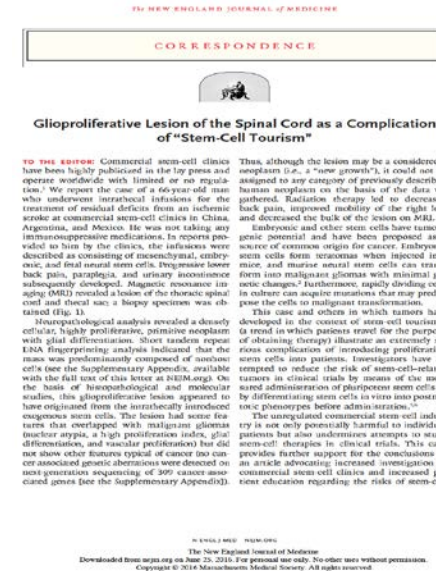
- Why? Evolution

“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



The Telegraph

Home	Video	News	World	Sport	Business	Money	Comment	Culture	Travel	Life
USA	Asia	China	Europe	Middle East	Australasia	Africa	South America	Central Asia		
France	Francois Hollande	Germany	Angela Merkel	Russia	Vladimir Putin	Greece	Sp			

We help make your move easy
FREE Installation | Special Offers
1-hour Service Windows

TV, Internet
& Phone



HOME » NEWS » WORLD NEWS » EUROPE » GERMANY

Europe's largest stem cell clinic shut down after death of baby

Europe's largest stem cell clinic, which is at the centre of a scandal over the death of a baby given an injection into the brain, has been shut down.

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 (\$\$)

SHORT REPORT

No benefits from experimental treatment with olfactory ensheathing cells in patients with ALS

Sanne Piepers & Leonard H. van den Berg
Pages 328-330 | Received 09 Dec 2009, Accepted 28 Jan 2010, Published online: 03 May 2010
[Download citation](#) <http://dx.doi.org/10.3109/17482961003663555>

[Full Article](#) [Figures & data](#) [References](#) [Citations](#) [Metrics](#) [Reprints & Permissions](#) [Get access](#)

Abstract

Cell based therapies may be promising options for treating ALS. These therapies aim at neuronal replacement or they may prevent dysfunctional motor neurons from dying. Conflicting results on transplantation of olfactory ensheathing cells (OECs) in ALS mouse models indicate that this technique is not yet ready to progress to clinical trials. A Chinese group has nevertheless treated ALS patients with OECs. We carried out a prospective study of seven patients who underwent OEC treatment in China, following them from four months before departure until one year after treatment. Muscle strength, level of daily functioning and respiratory capacity were measured at regular intervals. Three patients reported subjective positive effects directly after treatment. No individual objective improvement was measured, and outcome measures gradually declined in all patients. Two patients had severe side-effects. Based on our findings in these ALS patients who underwent experimental OEC treatment, we conclude that there are no indications that this treatment is beneficial.

Key words:: Amyotrophic lateral sclerosis, olfactory ensheathing cells, transplantation

Log in via your institution

- Shibboleth
- OpenAthens

Log in to Taylor & Francis Online

Enter your email
Enter your password

☐ Remember Me [Forgot password?](#)

[Log in](#)

Or purchase it *

ALS Amyotrophic Lateral Sclerosis
Volume 11 2010 - Issue 3

Article Purchase [Add to cart](#)
24 hours access for USD 54.00

Issue Purchase [Add to cart](#)
30 days access for USD 308.00

* Local tax will be added as applicable

Sample User
Medicine, Dentistry, Nursing & Allied Health Journals

CALL FOR PAPERS
Comprehensive
Child and Adolescent
Nursing
Building Evidence for Practice

MOST READ

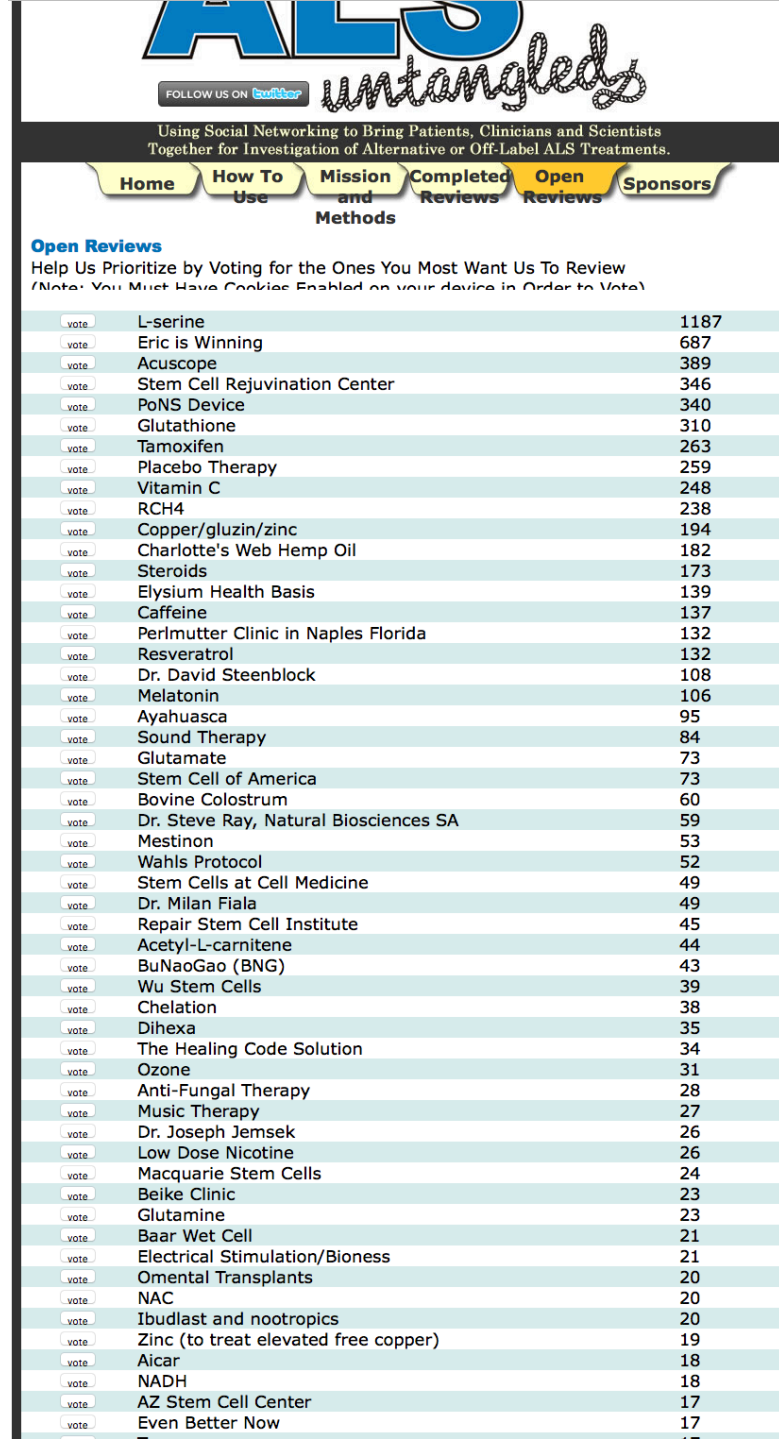
ALSUntangled

- 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



The screenshot shows the 'ALS untangled' website. At the top, it says 'Using Social Networking to Bring Patients, Clinicians and Scientists Together for Investigation of Alternative or Off-Label ALS Treatments.' Below this is a navigation bar with tabs: Home, How To Use, Mission and Methods, Completed Reviews, Open Reviews (highlighted), and Sponsors. Under the 'Open Reviews' tab, there is a heading 'Open Reviews' and a sub-heading 'Help Us Prioritize by Voting for the Ones You Most Want Us To Review (Note: You Must Have Cookies Enabled on your device in Order to Vote)'. Below this is a table listing various treatments with a 'vote' button and a count.

vote	Treatment	Count
<input type="button" value="vote"/>	L-serine	1187
<input type="button" value="vote"/>	Eric is Winning	687
<input type="button" value="vote"/>	Acuscope	389
<input type="button" value="vote"/>	Stem Cell Rejuvenation Center	346
<input type="button" value="vote"/>	PoNS Device	340
<input type="button" value="vote"/>	Glutathione	310
<input type="button" value="vote"/>	Tamoxifen	263
<input type="button" value="vote"/>	Placebo Therapy	259
<input type="button" value="vote"/>	Vitamin C	248
<input type="button" value="vote"/>	RCH4	238
<input type="button" value="vote"/>	Copper/gluzin/zinc	194
<input type="button" value="vote"/>	Charlotte's Web Hemp Oil	182
<input type="button" value="vote"/>	Steroids	173
<input type="button" value="vote"/>	Elysium Health Basis	139
<input type="button" value="vote"/>	Caffeine	137
<input type="button" value="vote"/>	Perlmutter Clinic in Naples Florida	132
<input type="button" value="vote"/>	Resveratrol	132
<input type="button" value="vote"/>	Dr. David Steenblock	108
<input type="button" value="vote"/>	Melatonin	106
<input type="button" value="vote"/>	Ayahuasca	95
<input type="button" value="vote"/>	Sound Therapy	84
<input type="button" value="vote"/>	Glutamate	73
<input type="button" value="vote"/>	Stem Cell of America	73
<input type="button" value="vote"/>	Bovine Colostrum	60
<input type="button" value="vote"/>	Dr. Steve Ray, Natural Biosciences SA	59
<input type="button" value="vote"/>	Mestinon	53
<input type="button" value="vote"/>	Wahls Protocol	52
<input type="button" value="vote"/>	Stem Cells at Cell Medicine	49
<input type="button" value="vote"/>	Dr. Milan Fiala	49
<input type="button" value="vote"/>	Repair Stem Cell Institute	45
<input type="button" value="vote"/>	Acetyl-L-carnitine	44
<input type="button" value="vote"/>	BuNaoGao (BNG)	43
<input type="button" value="vote"/>	Wu Stem Cells	39
<input type="button" value="vote"/>	Chelation	38
<input type="button" value="vote"/>	Dihexa	35
<input type="button" value="vote"/>	The Healing Code Solution	34
<input type="button" value="vote"/>	Ozone	31
<input type="button" value="vote"/>	Anti-Fungal Therapy	28
<input type="button" value="vote"/>	Music Therapy	27
<input type="button" value="vote"/>	Dr. Joseph Jemsek	26
<input type="button" value="vote"/>	Low Dose Nicotine	26
<input type="button" value="vote"/>	Macquarie Stem Cells	24
<input type="button" value="vote"/>	Beike Clinic	23
<input type="button" value="vote"/>	Glutamine	23
<input type="button" value="vote"/>	Baar Wet Cell	21
<input type="button" value="vote"/>	Electrical Stimulation/Bioness	21
<input type="button" value="vote"/>	Omental Transplants	20
<input type="button" value="vote"/>	NAC	20
<input type="button" value="vote"/>	Ibudlast and nootropics	20
<input type="button" value="vote"/>	Zinc (to treat elevated free copper)	19
<input type="button" value="vote"/>	Aicar	18
<input type="button" value="vote"/>	NADH	18
<input type="button" value="vote"/>	AZ Stem Cell Center	17
<input type="button" value="vote"/>	Even Better Now	17

Many Others



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)

	Grade					
Evidence category	U	F	D	C	B	A
Mechanistic plausibility	Unknown	Implausible; would violate known principles or laws of biology	Acts on a biological mechanism but it is not clear than this mechanism is relevant in ALS	Theoretically and plausibly acts on an ALS-relevant mechanism in humans	Shown in a peer-reviewed publication to act on a relevant mechanism in pre-clinical model(s)	Shown in a peer-reviewed publication to act on a relevant mechanism in humans
Pre-clinical models (animal or cell models recognized by ALSUntangled reviewers to be relevant to ALS)	None	The only studies available show no benefit	One or more non-peer reviewed studies reporting benefits (published on a website or in an abstract)	One or more peer-reviewed publication(s) reporting benefits in flawed studies (*)	One peer-reviewed publication reporting benefits in a well-designed study (*)	Two or more peer-reviewed publications reporting benefits in well-designed studies (*)
Patient case reports	None	The only reports available show no benefit	Subjective report(s) of benefit without validated diagnoses and/or benefits	One unpublished report of benefit with validated diagnosis and benefits	More than one unpublished report of benefit with validated diagnosis and benefits	One or more peer-reviewed publications reporting benefits with validated diagnosis and benefits
Patient trials	None	The only trials available show no benefit	One or more peer-reviewed publications reporting benefits in a flawed trial (**)	One or more peer-reviewed publications reporting benefits in a well-designed randomized, blinded, placebo-controlled phase I or II trial	One peer-reviewed publication reporting benefits in a well-designed randomized, blinded, placebo-controlled phase III trial	Two or more peer-reviewed publications describing benefits in well-designed randomized, blinded placebo-controlled phase III trials
Risks (harms that occurred on this treatment)	Unknown	At least 5% of exposed patients experienced death or hospitalization	More than 0% but less than 5% of exposed patients experienced death or hospitalizations	At least 10% of exposed patients experienced harms (no hospitalizations or deaths)	More than 0% but less than10% of exposed patients experienced harms (no hospitalizations or deaths)	No exposed patients appear to have experienced harms

ALSUntangled Table Of Evidence (TOE)

	Grade					
Evidence category	U	F	D	C	B	A
Mechanistic plausibility	Unknown	Implausible; would violate known principles or laws of biology	Acts on a biological mechanism but it is not clear than this mechanism is relevant in ALS	Theoretically and plausibly acts on an ALS-relevant mechanism in humans	Shown in a peer-reviewed publication to act on a relevant mechanism in pre-clinical model(s)	Shown in a peer-reviewed publication to act on a relevant mechanism in humans
Pre-clinical models (animal or cell models recognized by ALSUntangled reviewers to be relevant to ALS)	None	The only studies available show no benefit	One or more non-peer reviewed studies reporting benefits (published on a website or in an abstract)	One or more peer-reviewed publication(s) reporting benefits in flawed studies (*)	One peer-reviewed publication reporting benefits in a well-designed study (*)	Two or more peer-reviewed publications reporting benefits in well-designed studies (*)
Patient case reports	None	The only reports available show no benefit	Subjective report(s) of benefit without validated diagnoses and/or benefits	One unpublished report of benefit with validated diagnosis and benefits	More than one unpublished report of benefit with validated diagnosis and benefits	One or more peer-reviewed publications reporting benefits with validated diagnosis and benefits
Patient trials	None	The only trials available show no benefit	One or more peer-reviewed publications reporting benefits in a flawed trial (**)	One or more peer-reviewed publications reporting benefits in a well-designed randomized, blinded, placebo-controlled phase I or II trial	One peer-reviewed publication reporting benefits in a well-designed randomized, blinded, placebo-controlled phase III trial	Two or more peer-reviewed publications describing benefits in well-designed randomized, blinded placebo-controlled phase III trials
Risks (harms that occurred on this treatment)	Unknown	At least 5% of exposed patients experienced death or hospitalization	More than 0% but less than 5% of exposed patients experienced death or hospitalizations	At least 10% of exposed patients experienced harms (no hospitalizations or deaths)	More than 0% but less than 10% of exposed patients experienced harms (no hospitalizations or deaths)	No exposed patients appear to have experienced harms

Can help PALS validate, centralize both positive and negative anecdotes, temper conclusions based on natural history of disease

Completed Reviews

Table of Evidence Grades
(click here for explanation)

	Mechanism	Pre-Clinical	Cases	Trials	Risks
Iplex	D	B	B	D	F
The Hickey Wellness Center	D	U	C	U	B
Stem cell transplants at the Hospital San Jose Tecnológico de Monterrey	D	U	U	D	F
The XCell-Center	C	U	D	U	D
The Stowe/Morales ALS Protocol	C	U	U	U	U
Marty Murray's Method	F	U	D	U	U
Hyperimmune Goat Serum for ALS	C	C	D	D	C
Low dose naltrexone for ALS	D	U	D	U	B
Spirulina (blue green algae) as a treatment for ALS	C	C	U	U	A
Luteolin and Lutimax	C	U	D	U	B
NuTech Mediworld	C	U	F	U	U
Dean Kraft, Energy Healer	F	U	C	U	A
Bee Venom	C	C	D	U	B
Mototab	C	U	U	U	U
Coconut Oil	C	U	D	U	B
Cannabis	C	C	D	F	U
"When ALS Is Lyme"	D	U	D	U	B
Apoaequorin (Prevagen)	C	U	D	U	B
Sodium Chlorite					
A. NP001	A	D	U	C	B
B. WF10	A	D	D	U	C
C. ORAL	F	U	D	U	F
Deanna Protocol	B	C	D	U	B
Fecal Transplants	D	U	D	U	B
Propofol	C	U	D	U	D
Rife Machine and Retroviruses	F	U	D	U	B
Vitamin D	C	C	F	D	B
Ursodiol	C	U	D	D	C
Lunasin	C	U	C	U	B
Precision Stem Cell	B	C	D	U	C
Acupuncture	B	C	A	D	D
Mito Q	B	C	D	U	C
Methylcobalamin	A	C	D	D	B
Protandim	A	U	C	U	B
Gluten-Free Diet	C	U	A	U	C
Endotherapy	D	C	D	D	U
GM604	D	D	D	U	U
Hyperbaric Oxygen	B	C	C	F	D
Accilion	F	U	C	U	C
Inosine	C	U	D	U	C
L-Serine	B	C	D	D	C
Acuscope	D	U	F	U	B

Reviews published in ALS-FTD and on our website

All free Open Access

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

Explore

> Latest articles

> Most read articles

> Most cited articles

> Open access articles

Most read articles

Review article

ALS Untangled No. 20: The Deanna Protocol >

The ALSUntangled Group

Published online: 14 May 2013

VIEWS: 23782

Case report

ALSUntangled 15: Coconut Oil >

The ALSUntangled Group

Published online: 8 May 2012

VIEWS: 13159

Research article

ALSUntangled No. 31: Protandim >

The ALSUntangled Group

Published online: 28 Sep 2015

VIEWS: 10761

Research article

ALSUntangled No. 26: Lunasin >

The ALSUntangled Group

Published online: 28 Nov 2014

VIEWS: 10623

Brief report

ALSUntangled No. 16: Cannabis >

The ALSUntangled Group

Published online: 28 May 2012

VIEWS: 8268

Brief report

ALSUntangled No. 8: Low dose naltrexone for ALS >

VIEWS: 6769

Top 9 most read articles in ALS-FTD -More than 90K downloads

<http://www.tandfonline.com/action/showMostReadArticles?journalCode=iafd20>

Lessons Learned-Proponents

- Some are snake oil salesmen
 - <http://lamesa.patch.com/articles/larry-stowe-sought-on-arrest-warrant-in-texas-inafmous-on-60-minutes>
 - http://www.cbsnews.com/2100-18560_162-6402854.html?pageNum=7&tag=contentMain;contentBody
 - *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/>
- More are “true believers”
- Many have mannerisms that mainstream doctors should adapt
 - Optimism, respect, responsiveness
 - *ALS*2009;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)



- www.deankrafthealer.com/Dean-Kraft-Fox-TV-Sightings-May-1-1992.html
- <http://informahealthcare.com/doi/pdf/10.3109/21678421.2014.959297>

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

• *Neurol Ther* 2014;17:15

Clinical research

The role of serendipity in drug discovery

Thomas A. Ban, MD, FRCP(C)



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. It has also played a role in the discovery of several drugs that have had an impact on the development of psychiatry. "Serendipity" in drug discovery implies the finding of one thing while looking for something else. This was the case in six of the twelve serendipitous discoveries reviewed in this paper, ie, aniline purple, penicillin, lysergic acid diethylamide, meprobamate, chlorpromazine, and imipramine. In the case of three drugs, ie, potassium bromide, chloral hydrate, and lithium, the discovery was serendipitous because an utterly false rationale led to correct empirical results; and in case of two others, ie, iproniazid and sildenafil, because valuable indications were found for these drugs which were not initially those sought. The discovery of one of the twelve drugs, clordiazepoxide, was sheer luck.

© 2006, LLS SAS. *Dialogues Clin Neurosci* 2006;8:335-345.

Keywords: chloral hydrate; chlorpromazine; imipramine; iproniazid; lithium; lysergic acid diethylamide; meprobamate; penicillin; serendipity; sildenafil.

Author affiliations: Emeritus Professor of Psychiatry, Vanderbilt University, Nashville, Tenn, USA.

Address for correspondence: Prof Thomas A. Ban, 1177 Yonge Street, Suite 607, Toronto, Ontario, Canada M4T 2Y4 (e-mail: tmb@alisonm.net)

Copyright © 2006 LLS SAS. All rights reserved.

335

www.dialogues-cns.org

Definition of serendipity

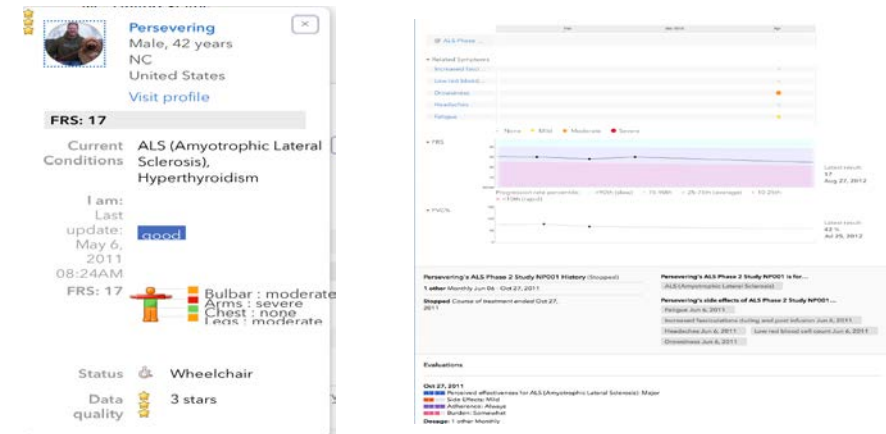
Serendip is the old Arabic name for Ceylon, now known as Sri Lanka. The origin of the word "serendipity" is in a Persian fairy tale, *The Three Princes of Serendip*, whose traveling heroes were "always making discoveries, by accidents and sagacity, of things they were not in quest of."¹ In the 16th century, the tale was translated from Persian to Italian, and from Italian to French. Horace Walpole (1717-1797), an English man of letters, encountered it in a collection of oriental tales in French, and coined the English term "serendipity" in a letter to his friend, Horace Mann, dated June 28, 1754.²

Today, the word "serendipity" is a word that is used in everyday language. The *Oxford English Dictionary* defines it as "the faculty of making happy and unexpected discoveries by accident," and *Webster's New Collegiate Dictionary* as "the faculty of finding valuable or agreeable things not sought for."³ In *Siedman's Medical Dictionary* "serendipity" refers to "an accidental discovery," ie, "finding one thing while looking for something else."⁴ According to the Doctor Out of Zebulon column in the *Archives of Internal Medicine*, "serendipity signifies a mental state in which serenity and stupidity are blended," as for example, "the serendipity of a cow chewing its cud under a shady tree," or "the sort of thing that happens to you when on a dull day collecting fossils you find instead a beautiful woman who proves to be neither geologist nor archeologist."⁵ However, this definition is erroneous, at least insofar as scientific discoveries are concerned. No scientific discovery has ever been made by pure luck. All happy accidents in science have one point in common: "each was recognized, evaluated and acted upon in the

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)



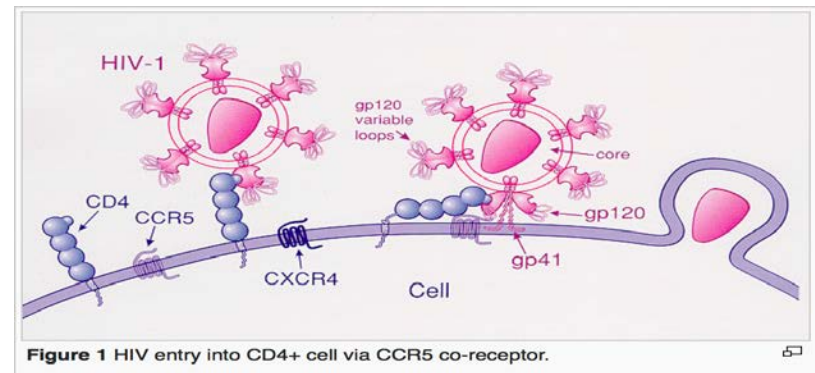
- First R.O.A.R. Trial (Lunasin) enrolled at a record pace, interim results at <https://f1000research.com/posters/5-2916>

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- Δ 32 that impairs viral entry
 - Maraviroc (Pfizer) first FDA approved CCR5 antagonist



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.)

	Cases	Controls	Statistical test	Result
Age	47.6 (15.2)	53.8 (11.8)	t= 2.87	p= .0041
% Male	80.0	60.3	X ² = 4.85	p= .0277
% Black	11.8	1.6	X ² = 10.7	p= .0011
% With family history of ALS	10.5	14.8	X ² = 0.266	p= .6059
% Limb onset	96.3	73.8	X ² = 7.06	p= .0079
Ambulation score progression	-1.69 (2.07)	-1.07 (1.75)	t= 1.83	p= .0670

- 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.)

AOT	OR	CI	Statistical Test	Result
Luteolin	450	59.9-3,380	$\chi^2 = 35.3$	$p < .0001$
Curcumin	300	47.1-1910	$\chi^2 = 36.5$	$p < .0001$
Azathioprine	150	28.2-796	$\chi^2 = 34.6$	$p < .0001$
Copper	32.1	7.07-145	$\chi^2 = 20.2$	$p < .0001$
Glutathione	24.2	5.40-108	$\chi^2 = 17.3$	$p < .0001$
Vitamin D	6.74	2.42-18.8	$\chi^2 = 13.3$	$p = .0003$

- 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 ($p < .0004$).

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

