



# ALSUntangled: Help for the Internet Buyers' Club

*Richard Bedlack MD PhD*

*Duke ALS Clinic*

*Durham NC, USA*

# Background-Need

- Although we now have many treatments, ALS usually remains disabling and life-shortening
- People living with ALS (PALS) understandably want access to experimental treatments



ALS patients and their families rallied for expanded access to experimental drugs in Washington, D.C. on May 11, 2015. (Courtesy of Lina Clark)



Demonstrators on their way to Biogen headquarters during a rally for Lisa Stockman-Mauriello, in Cambridge, Massachusetts, on March 30. Photographer: Jessica Rinaldi/The Boston Globe/Getty Images

# 3 Main Options for Accessing Experimental ALS Treatments

*(Curr Treat Options Neurol 2021;23:40)*

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Clinical Trials

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Expanded Access Programs (EAPs)

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Self-experimentation with  
alternative and off-label treatments

# Clinical Trials

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- Clinical Trials are my preferred pathway for this, because:
  - Products plausible, pure
  - Informed consent
  - Oversight (FDA, IRB, DSMB)
  - Rigorous data collection
  - Benefits to patients (hope, altruism, medical)
    - *Cancer* 1985;56:1710-1718
    - *Radiology* 1995;197:859-862
    - *Clin Invest Med* 1996;19:179-183
    - *Oncol Nurs Forum* 1997;24:1411-1416
    - *J Pediatr* 1999;134:151-155
    - *J Clin Epidemiol* 2001;54:217-224
    - *Controlled Clin Trials* 2003;24:341-352
    - *J Am Coll Surg* 2013;216:774-781

# Problems with Trials

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- There aren't nearly enough of them
- They are geographically restricted
  - *Clin Invest 2014;4:373–380*
- Most patients will not qualify
  - Inclusion criteria getting more and more narrow
    - Targeting specific disease subtypes
      - *ex. NEJM 2022;387:1099-1110*
    - Enrolling patients most likely to show signal on specific outcomes
      - *ex. Lancet Neurol 2017;16:505-512*
- Design features not always acceptable to or feasible for patients
  - *ALS 2008;9:257-265*
  - *ALS 2010;11:502-507*

# EAPs

*(Curr Treat Options Neurol 2021;23:40)*

- Great option for those who cannot qualify for trials; same products, oversight, some data collection
- But
  - There aren't nearly enough of them (even less spots than trials)
  - They are geographically restricted (even more so than trials)
  - Some patients will not qualify



# Self-Experimentation

- Up to 99% of PALS use this path  
(*Evid Based Complement Alternat Med 2013;2013:613596*)
  - Via MD prescription
  - Via FDA Personal Importation Policy  
(<https://www.fda.gov/industry/import-basics/personal-importation>)
  - Via “Buyers Club”
  - Via Internet

Scene from 2013  
movie “The Dallas  
Buyers Club”



February 4th, 2013 - by Jessica Espinoza

Coconut Oil Offers Hope For Those Suffering From ALS, Alzheimer's, and Parkinson's

ALS

Alzheimer's

coconut oil

parkinson's

**STEM CELL OF AMERICA**  
The Future is Already Here

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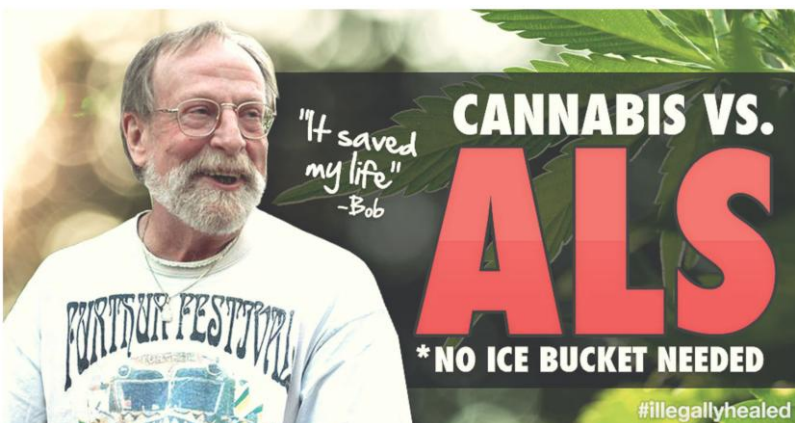


New Stem Cell Treatment


### ALS Breakthrough

- ▶ No known negative side effects
- ▶ Painless Procedure
- ▶ Limited Space Available
- ▶ Commonly, significant positive results are seen in three to six months

Contact Us Now We Can Help!




**THE DEANNA PROTOCOL®**  
**Hope for ALS**  
and Other Neurological Conditions



Vincent M. Tedone, M.D.  
Deanna Tedone-Gage  
Chiara Tedone

**ALS OR LYME ?**

When you get a diagnosis of ALS Doctor's are giving you a DEATH sentence. You feel like you have ALREADY died.



Many LYME disease patients are often misdiagnosed with ALS. Get evaluated for LYME disease if you have ALS. You have nothing to lose and a life to GAIN !

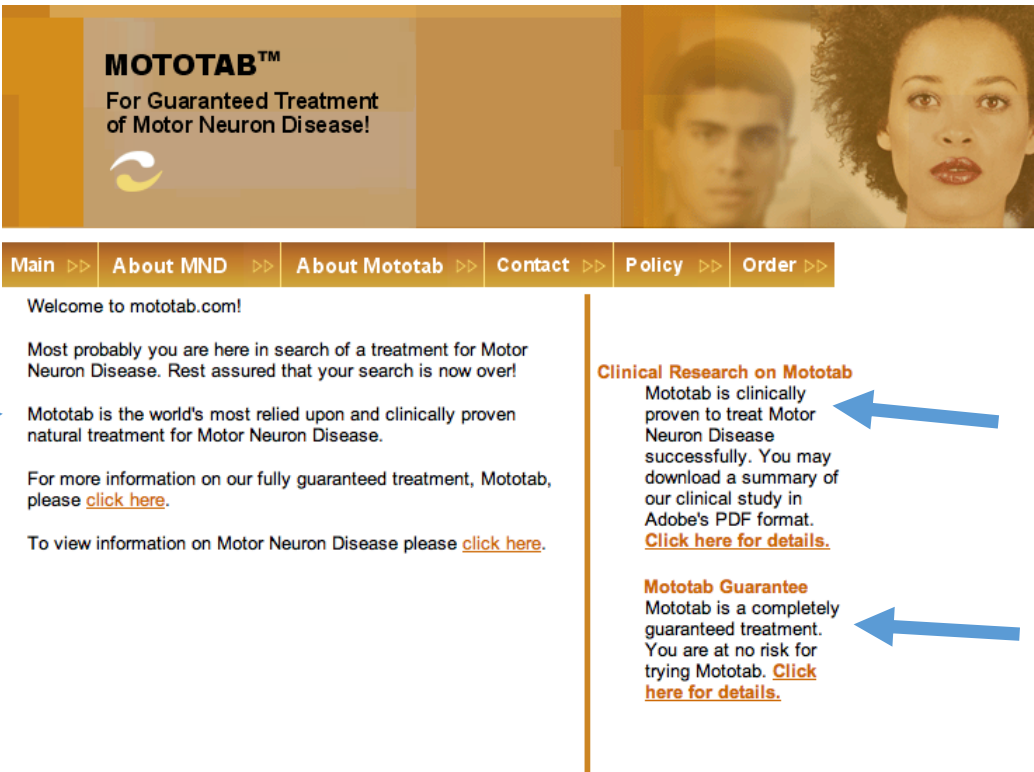
LYME DISEASE POSTERS  
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Many “alternative and off label” treatments (AOTs) currently being advertised on the Internet for ALS



# AOTs on the Internet

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

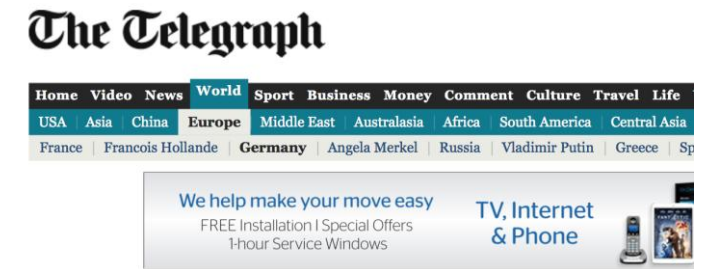
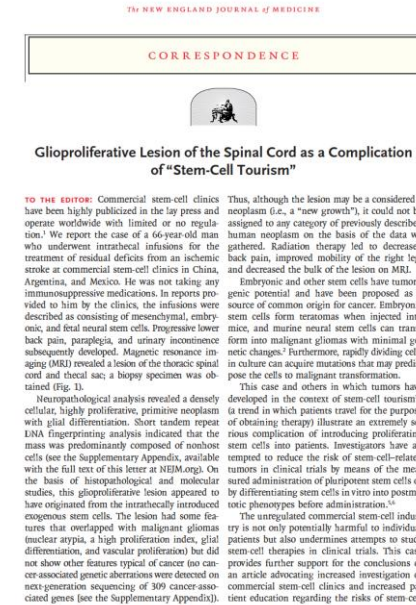


The screenshot shows the Mototab website with a header banner featuring the text "MOTOTAB™ For Guaranteed Treatment of Motor Neuron Disease!" and a logo. Below the banner is a navigation menu with links: Main >>, About MND >>, About Mototab >>, Contact >>, Policy >>, and Order >>. The main content area includes a welcome message, a paragraph 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: "click here" for more information and "click here" to view information on Motor Neuron Disease. On the right side, there are two sections: "Clinical Research on Mototab" which states that Mototab is clinically proven to treat Motor Neuron Disease successfully and provides a link to download a summary of the clinical study, and "Mototab Guarantee" which states that Mototab is a completely guaranteed treatment and provides a link for details. Blue arrows point from the list of claims on the left to these specific sections on the website.

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# Underappreciated Harms from AOTs

- Financial
  - AOTs can cost hundreds, thousands, hundreds of thousands of dollars
    - *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*



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.

# 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

**ALSUntangled** reviews alternative and off label treatments, with the goal of helping people with ALS make more informed decisions about them.



**About Our  
Method**



**Completed  
Reviews**



**Future Reviews**





# Inputs from PALS, CALS

- >500 suggested AOTs, listed on Future Reviews section of our website ([www.alsuntangled.org](http://www.alsuntangled.org))
- Prioritization
  - Votes
  - Multiplier
    - 0 if we cannot find any useful disclosable information on the AOT
    - 1 if we understand what the AOT is but cannot find a published ALS trial or case series on it
    - 2 if we can find at least 1 published ALS clinical trial or case series on it

## Future Reviews

Here you will find AOTs that patients and families around the world have asked us to review in the future. We are working hard to get these done as quickly as we can but it does take a lot of time to complete a thorough review. We invite you to cast up to one (1) vote for each item below. More information coming soon.

Vote	Treatment ▼	Multiplier ▼	Votes ▼	Final Priority ▼
<a href="#">Vote</a>	Infrared Sauna	1	1748	1748
<a href="#">Vote</a>	Nadir's ALS Remission Protocol	1	1407	1407
<a href="#">Vote</a>	Dr. David Steenblock	1	1249	1249
<a href="#">Vote</a>	Steroids	2	601	1202
<a href="#">Vote</a>	Caffeine	1	667	667
<a href="#">Vote</a>	Tamoxifen	2	328	656
<a href="#">Vote</a>	Lions Mane	1	591	591
<a href="#">Vote</a>	Stem Cells at "Hanyang University in South Korea"	1	577	577
<a href="#">Vote</a>	Placebo Therapy	2	276	552
<a href="#">Vote</a>	Melatonin	1	520	520
<a href="#">Vote</a>	Ozone	1	517	517
<a href="#">Vote</a>	Rituximab	1	431	431
<a href="#">Vote</a>	Inhaled Insulin	1	407	407
<a href="#">Vote</a>	PoNS Device	1	393	393
<a href="#">Vote</a>	Vitamin C	1	388	388
<a href="#">Vote</a>	Astaxanthin	1	366	366
<a href="#">Vote</a>	Charlotte's Web Hemp Oil	1	340	340
<a href="#">Vote</a>	Ibuprofen and nootropics	2	158	316
<a href="#">Vote</a>	Niagen	1	306	306

Many Others





# Reviews

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- Team
  - >130 members, 11 countries (USA, Canada, Ireland, Israel, Spain, Thailand, Sweden, Poland, France, Russia, Australia)
- 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 than 10% of exposed patients experienced harms (no hospitalizations or deaths)	No exposed patients appear to have experienced harms

# Outputs

- Reviews crowd-sourced, peer-reviewed, ultimately published in ALS-FTD
  - 78 published so far
  - All Free Open Access
  - TOE grades, PDFs posted under Completed Reviews on our website
- Updates on older reviews (\*)
- Partnered with CReATe to make podcasts (<https://podcasts.apple.com/us/podcast/create-podcast/id1356626499?uo=4>)
- Spanish, Italian translations available

Many Others



## Completed Reviews

Here you will find our published reports on AOTs, along with the grades we gave each of them in different categories, short summaries and even podcasts. Click on the name of the review to open the published report, or click on the podcast link to listen to a short interview about it. When new information about an AOT comes out after our published review, we update the summary and the assigned grades accordingly. Summaries and grades that have been updated since a published review are annotated with an asterix.

Click on any completed review title or letter grade below for detailed information. Click on any column header ("Treatment", "Mechanism", etc.) to sort the entire table by that column. In addition, you can [click here to view the complete table of evidence](#).

Treatment ▼	Podcast	Mechanism ▼	Pre-Clinical ▼	Cases ▼	Trials ▼	Risks ▼
<a href="#">Psilocybin (2025)</a>		C	U	U	U	F
<a href="#">WAHLS Protocol (2024)</a>		C	U	U	U	C
<a href="#">PoNS Device (2024)</a>		U	U	U	U	C
<a href="#">Ashwagandha (2024)</a>		B	A	C	U	B
<a href="#">Lions Mane (2024)</a>		B	U	F	U	B
<a href="#">Insulin (2023)</a>		C	B	U	U	F
<a href="#">Nuedexta (2023)</a>		B	U	A	C	C
<a href="#">Caffeine (2023)</a>		A	C	F	U	B
<a href="#">Astaxanthin (2023)</a>		A	U	C	U	B
<a href="#">Ozone (2022)</a>		A	D	C	U	D
<a href="#">Rituximab (2022)</a>		D	D	F	U	F
<a href="#">Glucocorticoid Corticosteroids (2022)</a>		D	F	B	F	C
<a href="#">Anti-Mycobacterial Antibiotics (2022)</a>		D	U	A	U	D
<a href="#">Butyrates (2022)</a>		A	A	C	U	C
<a href="#">Ketogenic Diets (2021) *</a> <i>Updated: Jan 2024</i>		B*	C*	A*	U*	D*
<a href="#">Vitamin C (2021)</a>		C	C	B	F	B
<a href="#">Melatonin (2021)</a>		A	C	B	U	B
<a href="#">Light Therapy (2021)</a>		D	C	D	U	A
<a href="#">Tamoxifen (2021)</a>		A	C	C	C	D



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## Most read articles

Explore the most read and trending articles published in Amyotrophic Lateral Sclerosis and Frontotemporal Dementia.

Last year	All time	Trending
Now showing: the most read articles of all time		
<input type="radio"/> Download Citation <input type="radio"/> Download PDFs		
<input type="radio"/> Review Article <b>ALS Untangled No. 20: The Deanna Protocol</b> >		
The ALSUntangled Group		52468 Views
Published online: 2 May 2013 (Vol.14, No.4, 2013)		17 CrossRef citations
		9 Altmetric
<input type="radio"/> Article <b>"ALS reversals": demographics, disease characteristics, treatments, and co-morbidities</b> >		
Daniel Harrison, Paul Mehta, Michael A. van Es, Elijah Stommel, Vivian E. Drory, Beatrice Nefussy, Leonard H. van den Berg, Jesse Crayle, Richard Bedlack & the Pooled Resource Open-Access ALS Clinical Trials Consortium		30403 Views
Published online: 2 Apr 2018 (Vol.19, No.7-8, 2018)		31 CrossRef citations
		32 Altmetric
<input type="radio"/> ALSUntangled: Introducing The Table of Evidence >		
The ALSUntangled Group		29796 Views
Published online: 27 Dec 2014 (Vol.16, No.1-2, 2015)		10 CrossRef citations
		1 Altmetric
<input type="radio"/> Article <b>ALSUntangled No. 31: Protandim</b> >		
The ALSUntangled Group		27229 Views
Published online: 28 Sep 2015 (Vol.17, No.1-2, 2016)		1 CrossRef citations
		11 Altmetric
<input type="radio"/> Article <b>ALSUntangled No. 26: Lunasin</b> >		
The ALSUntangled Group		24864 Views
Published online: 23 Sep 2014 (Vol.15, No.7-8, 2014)		6 CrossRef citations
		12 Altmetric
<input type="radio"/> Case Report <b>ALSUntangled 15: Coconut Oil</b> >		
The ALSUntangled Group		24164 Views
Published online: 8 May 2012 (Vol.13, No.3, 2012)		5 CrossRef citations
		9 Altmetric
<input type="radio"/> Article <b>ALSUntangled 44: curcumin</b> >		
Richard Bedlack & ALSUntangled Group		22393 Views
Published online: 1 Mar 2018 (Vol.19, No.7-8, 2018)		7 CrossRef citations
		2 Altmetric

# Success?

- Won multiple awards from patients, peers
- 8 of the top 10 most downloaded articles in the history of the ALS-FTD journal
  - Some individual reviews have >50,000 downloads
  - Collectively, >400,000 downloads
- Podcasts have >35,000 listens

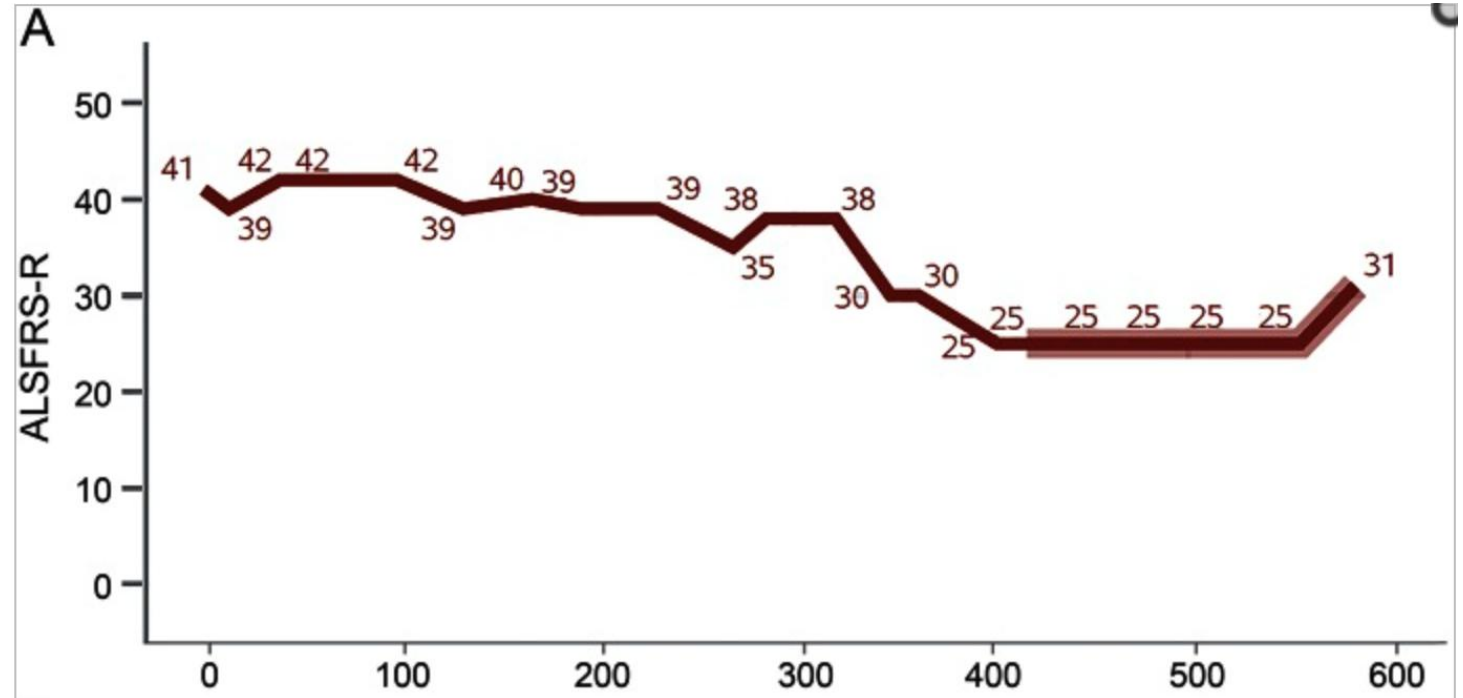
# Lessons Learned: Proponents

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- Motivations vary
  - Many are “true believers”
- They do some things that mainstream doctors need to learn from
  - Optimistic, hope-boosters
  - Respectful
  - Responsive

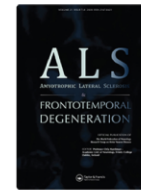
# Lessons Learned: Natural History

- Progression is not only variable between patients, it can also be quite variable in a single patient at different times
- Plateaus, small reversals not uncommon (*Neurology*. 2016 Mar 1;86(9):808-12)
- Dramatic ALS reversals can very rarely occur ([www.alsreversals.com](http://www.alsreversals.com))



# Lessons Learned: The Worst AOTs Share “Red Flags”

- Large out of pocket costs
- Advertised as effective for multiple incurable conditions with different causes
- Lack of safety and scientific oversight
- Absent or limited informed consent process
- Lack of an evidenced mechanism by which the intervention might help
- Absence of regularly measured validated outcomes
- Vague or no plan to present outcomes for peer review
- The only evidence of benefit is anecdotes
- Proponents have no relative training, presentations or publications
- Proponents portray themselves as victims, advise “divorce” from mainstream doctors



Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration



ISSN: (Print) (Online) Journal homepage: <https://www.tandfonline.com/loi/iafd20>

## ALSUntangled 56: “ten red flags”-things to be wary of in alternative or off-label products

The ALSUntangled Group

To cite this article: The ALSUntangled Group (2020) ALSUntangled 56: “ten red flags”-things to be wary of in alternative or off-label products, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 21:7-8, 642-647, DOI: [10.1080/21678421.2020.1765518](https://doi.org/10.1080/21678421.2020.1765518)

To link to this article: <https://doi.org/10.1080/21678421.2020.1765518>



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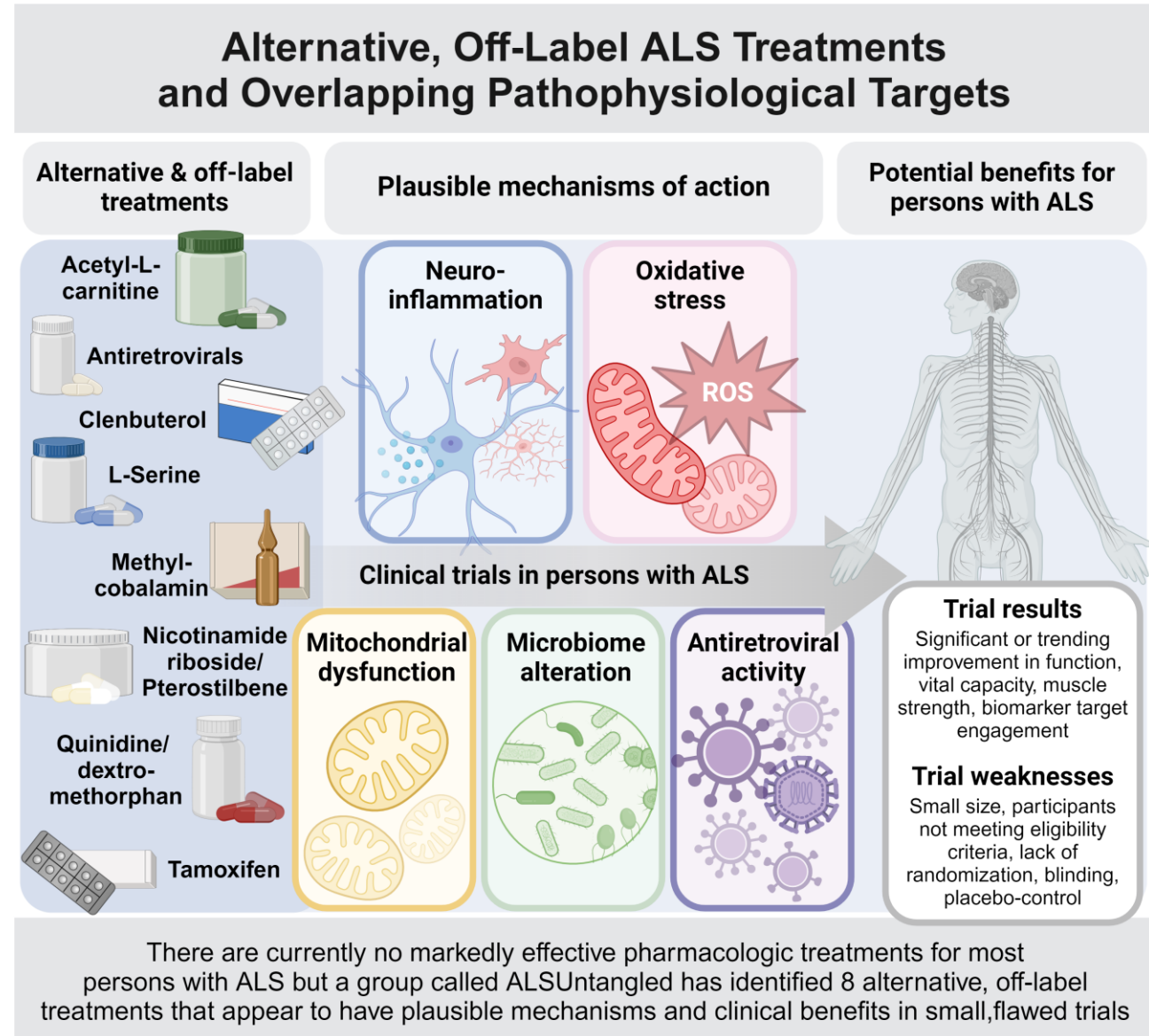


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# Lessons Learned: Some AOTs Warrant Further Testing

- (Annals of Neurology 2024;97:15-27)



How I Guide Patients in My Clinic  
Who Want to Experiment

# Step 1. Build a Foundation

- There are now many evidence and experience-based treatments for ALS (<https://www.uptodate.com/contents/disease-modifying-treatment-of-amyotrophic-lateral-sclerosis>; <https://www.uptodate.com/contents/symptom-based-management-of-amyotrophic-lateral-sclerosis?source=related> link )
  - We know these slow ALSFRS-R progression, reduce hospitalizations, improve quality of life, lengthen survival
- I encourage patients in my clinic to take advantage of these while they experiment with other things

## Step 2. Review Pathways for Experimentation (in My Preferred Order)

- Clinical Trials
- Expanded Access Programs
- Self-Experimentation with alternative and off-label products





# Step 3. For Those Who Must Self-Experiment...

- Just Starting
  - Add 1 new product at a time, starting with “top tier”
- Already on a large regimen
  - Remove products already shown not to work in ALS trials (ex. coQ10, vitamin C, vitamin E, glutathione), or those with lots of “red flags”
  - Remove products with overlapping mechanisms (ex. multiple antioxidants)
  - Add 1 new product at a time, starting with top tier or ones that have a mechanism that is not being targeted by the patient’s current regimen
- For each product, have a target dose, agreed upon outcomes, duration, stopping rules
  - Ideally the dose is determined by trials, biomarker studies, safety studies
  - Outcome I use: 50% slowing in ALSFRS-R progression over 6 months

# Conclusions

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- PALS want experimental options; while trials and EAPs are the preferred paths, “self experimentation” with AOTs will be the only option for most
- When it comes to AOTs, “The Truth Is Out There” but it isn’t always easy to find
- ALSUntangled brings PALS, clinicians & scientists together to systematically review and report on AOTs with a goal of PALS making more informed decisions
- I have learned several important lessons in this program, and I use these to guide my practice and approach to AOTs



# Thanks

