PERSPECTIVE

Untangling the ALS X-Files

Richard Bedlack explains how an open mind led him to some unusual places and unexpected lessons.

In the television drama series *The X-Files*, Fox Mulder's life changed when his sister Samantha disappeared. He believed she was kidnapped by aliens. The scepticism he encountered propelled him into a series of paranormal investigations.

My own 'Samantha' was a person I diagnosed with amyotrophic lateral sclerosis (ALS) who surprised me by passing up participation in a clinical trial in favour of self-experimenting with energy healing. Her decision was influenced by a story on the energy-healer's website describing someone with advanced ALS who had made a complete recovery.

I have since learned that most people with ALS self-experiment using alternative treatments¹. It is easy to see why: although symptomatic therapy has improved, mainstream medicine still has no way to stop or reverse this disabling, life-shortening disease. Like Mulder, patients and their families "want to believe" there is something better out there.

The Internet is loaded with unorthodox options for treating the disease. Proponents describe these as "guaranteed" and "perfectly safe". Their claims are commonly supported by anecdotes that are particularly compelling to non-scientists. Complicating matters further, the natural history of ALS progression is non-linear, characterized by spontaneous periods of stability and even small brief improvements². These plateaus and small reversals may be misinterpreted as treatment effects. And whereas potential benefits are being overestimated, underappreciated physical, financial and psychological harms often arise from self-experimentation³.

Self-experimenting patients may seek guidance from their neurologists, who can handle these conversations in different ways. Some take a paternalistic attitude, dismissing any discussion of alternatives as pointless or harmful. Some support autonomy, leaving the decision entirely up to the patient. Others try to engage in shared decision-making, discussing options and what evidence there might be of success. Shared decision-making is the model that most patients and physicians prefer, and is associated with better health outcomes⁴, but many physicians worry that it takes too much time.

In an attempt to support shared decision-making, in 2009 I started a programme called ALSUntangled (www.alsuntangled.com) which systematically reviews alternative ALS treatments. Patients and families send suggestions for reviews by e-mail and Twitter, and our team of 100 clinicians and scientists from 10 countries reviews each one, grading them across 5 categories: mechanistic plausibility, preclinical data, cases (anecdotes), trials and risks. Within each category, we assign a grade of A to F (A being the most favourable), with objective cut-offs for achieving each grade⁵. All reviews are eventually published with open access in the journal *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* and on our website. ALSUntangled reviews are the most downloaded articles in this journal's history.

Like Mulder's, my quest for the truth has been paved with unexpected lessons. Proponents of alternative treatments are not all snake-oil salesmen; some are true believers who think that their product works, but lack interest in or the knowledge for testing it. Some of the oddest-sounding treatments that patients have asked about, such as coconut oil and faecal transplants, actually have plausible mechanisms and should be examined in ALS trials. Most amazing of all, the dramatic ALS reversal described on the energy healer's website is real. I interviewed the patient myself and reviewed her medical records. And she is not alone. I have since validated 33 other remarkable ALS reversals.

There are three possible explanations for these reversals, which suggest new avenues of research. First, because there is no diagnostic test

for ALS, some patients might have had rare conditions that mimic the symptoms of ALS but could spontaneously improve. Antibody-mediated syndromes such as multi-focal motor neuropathy⁶, myasthenia gravis⁷ and coeliac disease⁸ are possibilities. I plan to screen the reversal patients for these diseases. Second, the patients might have genetic polymorphisms that confer resistance to ALS. There is a precedent for 'resistance' polymorphisms in the existence of a group of HIV 'elite controllers', who resist HIV infection despite repeated exposure. I will compare the genomes of people with ALS reversal to those of more typically progressing patients. Finally — and most tantalizingly — maybe their treatment regimens

actually worked. There are, after all, previous examples of patients serendipitously discovering successful treatments, such as Viagra and Nuedexta, used for other ailments. I am now conducting patient-centric pilot trials of the treatment regimens used by people with ALS reversal.

In trying to make sense of his sister's disappearance, Mulder eventually found proof of extraterrestrials. By helping patients and families to make more-informed decisions about self-experimentation, I have found new candidates for ALS trials and a small group of patients who seem to beat ALS. I am now trying to understand why these ALS reversals happened, and to make them happen more often. When backed by careful science, it is amazing where an open mind can lead. ■

Richard Bedlack is associate professor of neurology at Duke University in Durham, North Carolina.
e-mail: richard.bedlack@duke.edu

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