

Drug Repurposing - Challenges and Opportunities

Petra Kaufmann, M.D., M.Sc.

Director, Office of Clinical Research, NINDS

IOM Workshop on Genomics-Enabled Drug
Repositioning & Drug Repurposing

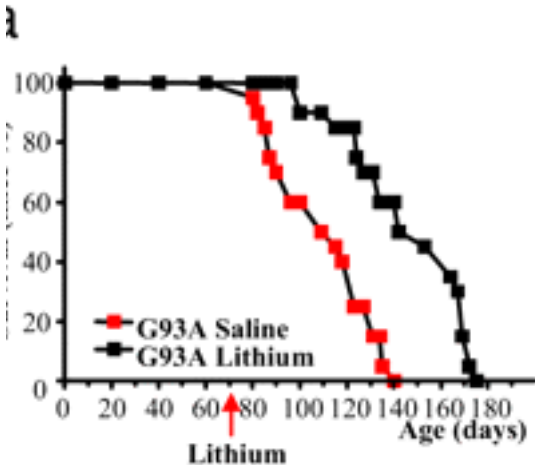
June 24, 2013

Washington, DC

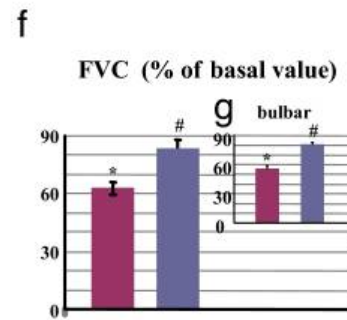
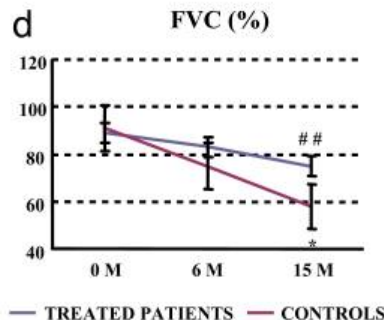
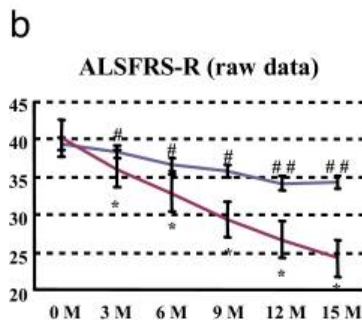
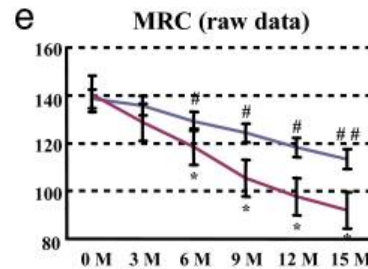
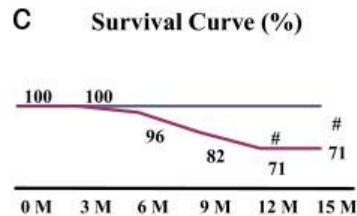
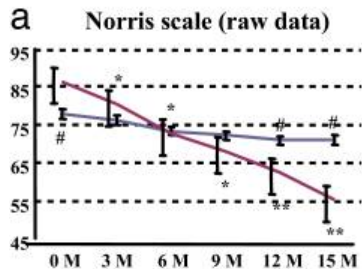
Outline

- Case studies from neurological disorders
 - ALS
 - SMA
- Lessons learned
 - Communication
 - Stakeholder collaboration
 - Strategies

Lithium for Amyotrophic Lateral Sclerosis



- Lithium is a mood stabilizer with presumed neuroprotective properties
- Lithium is thought to promote autophagy through the inhibition of the inositol-monophosphatase
- Increased survival in mouse studies (rigor?)



- Lithium was “repurposed” for ALS
- N=44, 16 active, 28 placebo, not double-blinded
- **“Lithium delays progression of ALS sclerosis”**

Fornai and colleagues, PNAS 2008;105:22052

Social Media and Lithium — patients like me

AMIA Ann. Symp Proc. 2008;
217–221. Frost and colleagues

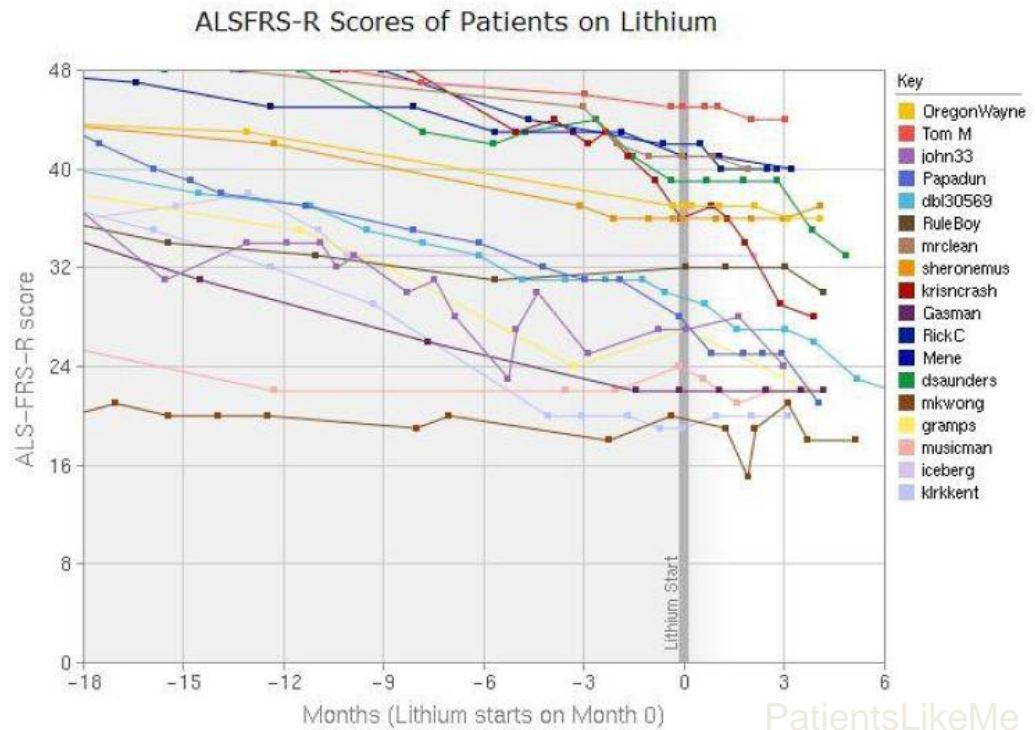


116 people report
taking lithium

Were people taking lithium
similar to those who did not
take lithium?

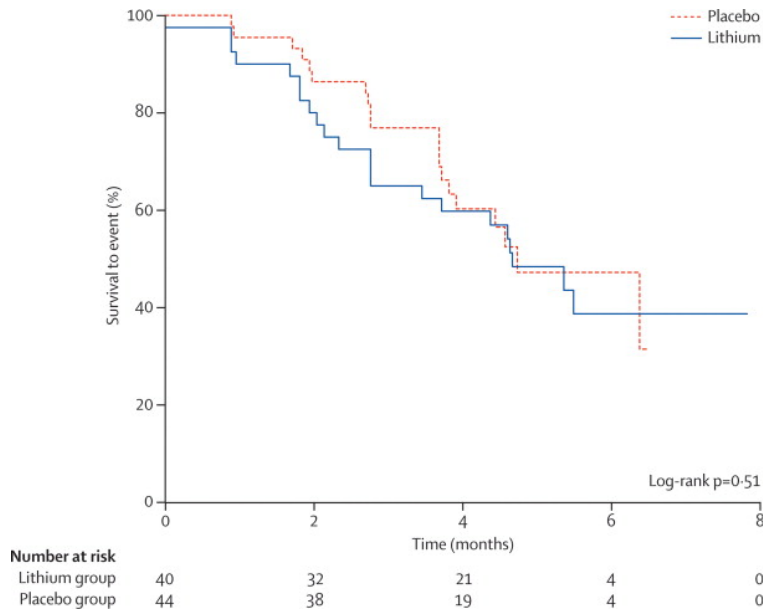


What happened to those
who stopped reporting their
progress?



“The study is what it is, whether you are a proponent or a critic makes no difference at the end of the day. Does it have its flaws? Sure. Does it have its redeeming points? Sure. It is a piece of evidence for people to use in their own judgments, nothing more, nothing less.”

Randomized, controlled, double-blind trial



Lancet Neurol. 2010;9:481. Aggarwal et al, Northeast and Canadian Amyotrophic Lateral Sclerosis consortia.

- US Phase 2 one arm trial, n=177
Miller et al, Neurology 2011
 - Editorial: Lithium treatment in amyotrophic lateral sclerosis: do we have enough trials?
DeCarvalho, Neurology 2011
 - Dutch Phase 2b trial, n=133, negative
Verstraete et al, J Neurol, Neurosurg, Psych 2012
 - UK phase 3 trial, n=214, negative
Morrison et al, Lancet Neurology 2013
 - The final chapter of the ALS lithium saga
Chio and Mora, Lancet Neurology 2013
- “the original trial of lithium in patients with ALS which suggested its **definite** efficacy as a treatment, was regarded as a substantial advance by patients, their families, and the ALS scientific and medical community.”

- Between January and June 2009, 84 patients were randomized
- Trial stopped for futility at the first pre-planned interim analysis
- Funded by NINDS, ALSA and the ALS Society of Canada

Re-purposing based on genetic etiology - Valproate for Spinal Muscular Atrophy

- SMN2 gene copies present in humans can produce functional SMN protein
- Drugable target
- Small molecule screens identified that valproic acid (VPA), phenylbutyrate (PB) and hydroxyurea (HU) can upregulate SMN expression
- VPA in SMA mouse models results in improved motor function, less degeneration, improvements at the NJM
- Patients asked their physicians for prescriptions
- Several open label “trials”
- One controlled trial for HU
- Two controlled trials for VPA
- Phase 1b and open label “trial” for PB)
- Several years
- Largely uncoordinated efforts

NCEs – not FDA approved

- Example: Niemann-Pick Type C
- Devastating lysosomal storage disease
- Inability of cells to metabolize and dispose of cholesterol and lipids
- Cyclodextrine promising in animal studies
- Several patients treated under “compassionate IND’s”
- Tension between individual use and the efforts to mount a trial

Approach: Social Media to Investigate Treatments

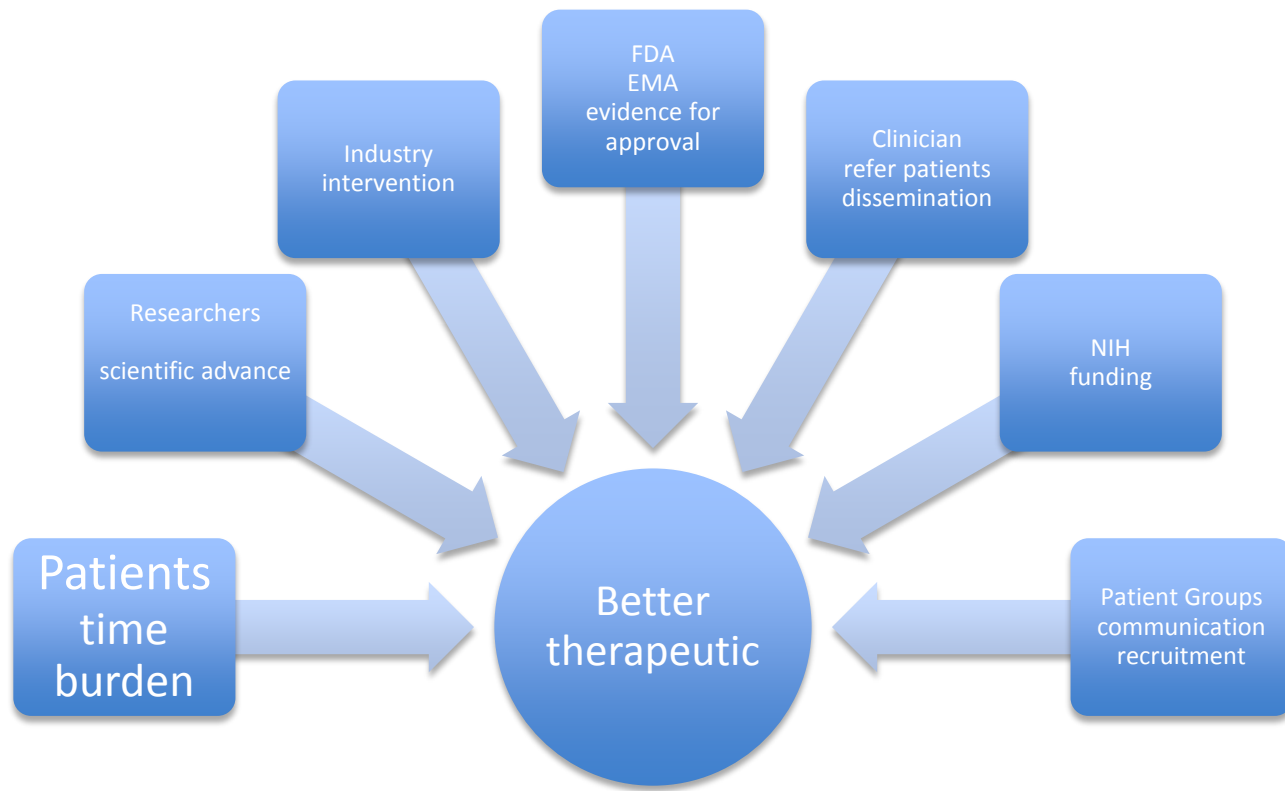
- **ALSUntangled (ALSU): A Scientific Approach to Off-Label Treatment Options for People with ALS Using Tweets and Twitters.**
Bedlack and Hardiman, ALS 2009;3:129
- **Patients tweet questions on alternative, off-label treatments (AOTs)**
- **AOT tweets are imported to NING where ALS clinician scientists can help investigate**
 - **What is offered? How much does it cost? What is the scientific rationale? Benefit/risks? First-hand knowledge**
 - **Published investigations:** Lyme, Iplex
 - Pending requests: Dr. Zannos Grekos' Stem Cell Clinic, Equilibrium Therapy, Pulsed Electromagnetic Fields, Bronx Project's Therapy, Hickey Wellness Center, The X-Cell Center, The Eric is Winning Regimen, Diaphragmatic Pacing

Prioritizing – Connecting Stakeholders with Opportunities

- **Problem:** genomics-enabled drugs compete with repurposed and novel interventions for opportunities
- **Example:** TREAT-NMD Advisory Committee for Therapeutics
 - multidisciplinary body that provides the neuromuscular community (clinicians, researchers, patient advocacy groups and industry) with independent and objective guidance on advancing new therapies (whether novel or repurposed) for neuromuscular diseases
 - transparent and consistent guidance
 - non-confidential summary for public

Approach: Public Engagement

- Give patients and clinicians a seat at the table
 - Concept development
 - Protocol working group
- Bi-directional communication
- Transparency
- Dialogue with the community
- Patient training opportunities



We need innovative models to connect stakeholders

- Clearing house
- Crowd sourcing
- Coordinators
 - Patient organizations
 - Funders

Conclusions

- Drug repurposing uncovers dysfunction in the clinical research enterprise
- The most important stakeholders, patients, are frustrated and often bypass the current process
- All stakeholders (patients, industry, researchers) ultimately have one goal – better therapeutics
- They need to find a new model with increased transparency and communication

Questions?

