

History Lesson: The dawn of the Prozac era

- The first “modern” antidepressant: a cultural phenomenon
 - Efficacy identical to existing tricyclic drugs
 - BUT, claimed to have advantages in tolerability, adherence, and overall cost
 - 60 times as expensive as generic alternatives
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Pragmatic effectiveness trial of starting fluoxetine vs. starting a tricyclic antidepressant

- Random assignment of initial antidepressant choice
- No restrictions on subsequent dose changes or medication switching
- Patients and physicians not blinded (but outcome assessments were)
- Comparison by initial assignment, regardless of switching or discontinuation
- Assessed adherence, clinical outcomes, and costs

What did we find?

- Adherence:
 - Less switching after starting with fluoxetine
 - But no difference in overall adherence
- Depression severity:
 - Identical outcomes at 6 months
 - Starting with desipramine led to slight advantage by 24 months
- Treatment costs:
 - Higher antidepressant costs after starting with fluoxetine
 - No difference in total health services costs

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But nobody cared by the time results were published.

That cat was out of the bag – and had taken over the whole room!

Time between first appearance of cat's nose and publication of effectiveness trial results:

- Our trial (Fluoxetine vs. TCAs)
 - Fluoxetine approved: 12/87
 - Trial started: 1/91; results published: 6/96
- ARTIST (Fluoxetine vs. Sertraline vs. Paroxetine)
 - Sertraline approved: 12/91
 - Trial started: 4/99; results published: 12/01
- CATIE (Older vs. newer antipsychotics)
 - Risperidone approved: 10/93
 - Trial started: 1/01; results published: 9/05

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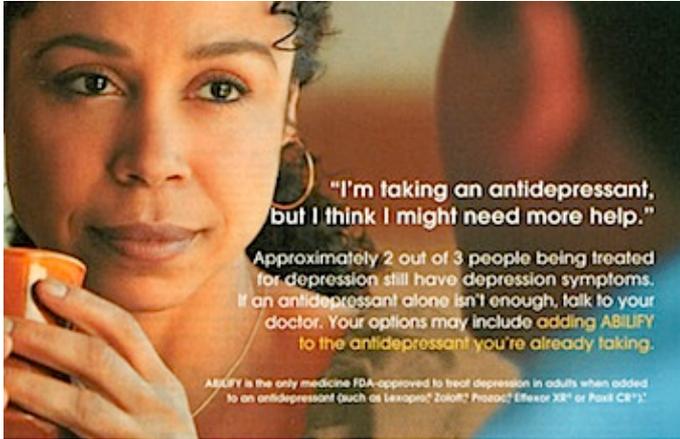
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Randomized trials: Delivering yesterday's weather forecast...tomorrow!

When the next Prozac comes along, we can expect:

- Claims for a fundamental advance in treatment
- Significantly higher costs (but claims for overall cost savings)
- Limited data comparing the new treatment to existing options
- Urgent need for practice and policy guidance - despite uncertainty

Fast forward to 2013:



"I'm taking an antidepressant, but I think I might need more help."

Approximately 2 out of 3 people being treated for depression still have depression symptoms. If an antidepressant alone isn't enough, talk to your doctor. Your options may include adding **ABILIFY** to the antidepressant you're already taking.

ABILIFY is the only medicine FDA-approved to treat depression in adults when added to an antidepressant (such as Lexapro®, Zoloft®, Prozac®, Effexor XR® or Paxil CR®).

IMPORTANT SAFETY INFORMATION:

Elderly patients with dementia-related psychosis (eg, an inability to perform daily activities due to increased memory loss) taking ABILIFY have an increased risk of death or stroke. ABILIFY is not approved for treating these patients.

Antidepressants can increase suicidal thoughts and behaviors in children, teens, and young adults. Serious mental illnesses are themselves associated with an increase in the risk of suicide. When taking ABILIFY call your doctor right away if you have new or worsening depression symptoms, unusual changes in behavior, or thoughts of suicide. Patients and their caregivers should be especially observant within the first few months of treatment or after a change in dose. Approved only for adults 18 and over with depression.

- Alert your doctor if you develop very high fever, rigid muscles, shaking, confusion, sweating, or increased heart rate and blood pressure, as these may be signs of a rare but potentially fatal condition called neuroleptic malignant syndrome (NMS).
- If you develop abnormal or uncontrollable facial movements, notify your doctor, as these may be signs of tardive dyskinesia (TD), which could become permanent.
- If you have diabetes or have risk factors or symptoms of diabetes, your blood sugar should be monitored. High blood sugar has been reported with ABILIFY and medicines like it. In some cases, extreme high blood sugar can lead to coma or death.
- Other risks may include lightheadedness upon standing, seizures, trouble swallowing, or impairment in judgment or motor skills. Until you know how ABILIFY affects you, you should not drive or operate machinery.

The common side effects in adults in clinical trials (>10%) include nausea, vomiting, constipation, headache, dizziness, an inner sense of restlessness or need to move (akathisia), anxiety, and insomnia. Tell your doctor about all the medicines you're taking, since there are some risks for drug interactions. You should avoid alcohol while taking ABILIFY.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please read the important information about ABILIFY on the adjacent page.

*Lexapro® (escitalopram oxalate), Zoloft® (sertraline HCl), Prozac® (fluoxetine hydrochloride), Effexor XR® (venlafaxine HCl), and Paxil CR® (paroxetine HCl) are trademarks of their respective companies.

IF AN ANTIDEPRESSANT ALONE ISN'T ENOUGH.



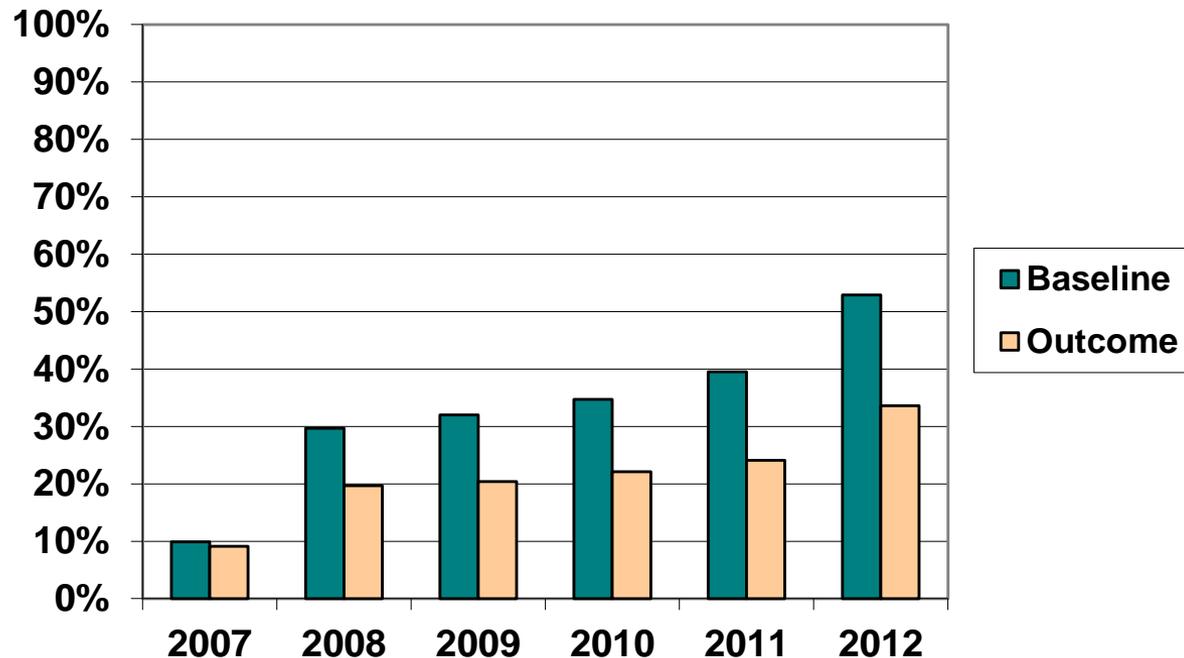
ABILIFY
(aripiprazole)
2 mg, 5 mg Tablet
www.abilify.com



Depression treatment data from four integrated health systems, 2008-2012:

- Enrolled population of approx. 5 million
- 680,000 episodes of depression treatment
- 510,000 patients

Proportion of antidepressant treatment episodes with standard assessment of severity (PHQ9)



Aripiprazole vs. alternative treatment changes

	2008	2009	2010	2011	Other Changes
Prescribed by specialist (vs. primary care)	75%	70%	63%	63%	29%
# prior antidepressants	3.3	3.1	3.0	3.0	2.3
% prior MH specialty care	63%	65%	62%	58%	40%
% prior psychiatric hosp.	11%	11%	7%	6%	3%
Baseline PHQ score	17.8	16.5	16.8	15.4	14.9
Mean prior PHQ scores (while on medication)	14.4	14.9	14.3	14.1	12.8

The goal: a real learning healthcare system:

“Each patient care experience naturally reflects the best available evidence, and, in turn, adds seamlessly to learning what works best in different circumstances.”

IOM Roundtable on Evidence-Based Medicine, 2008

A learning healthcare system means:

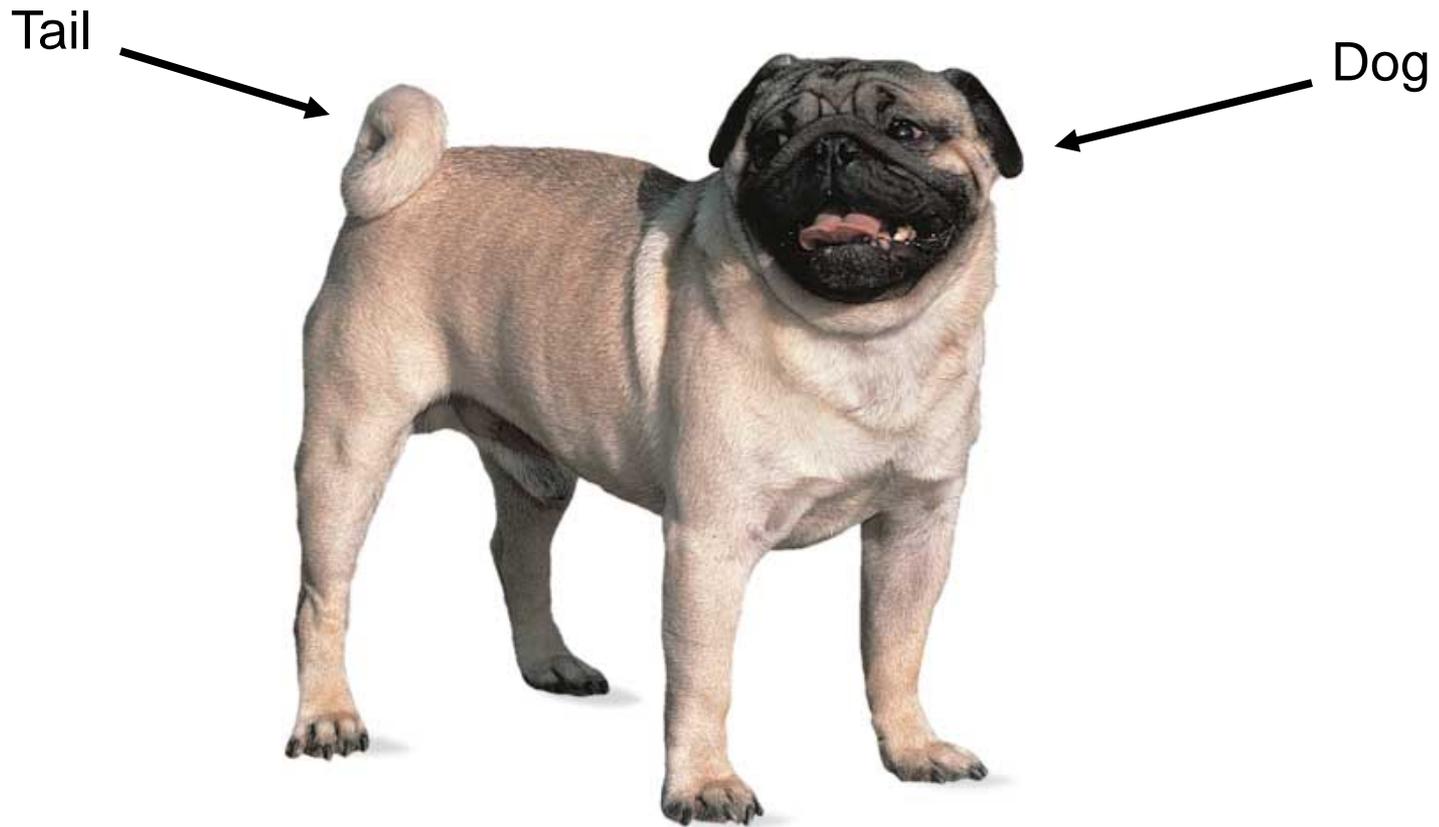
- All experience contributes to evidence
- It all happens continuously, in real time
- Clinical data = research data

Three challenges:

- Improving data quality
- Building a culture of transparency and trust
- Reforming the business model of research

All 3 are cultural challenges, not technical ones.

Where is the real data quality problem?



Where is the real data quality problem?

Tail



Dog



If the data aren't good enough for research,



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Tail



If the data aren't good enough for research,



Dog



...they certainly aren't good enough for taking care of patients.

It's not about research data quality.
It's about clinical data quality!

The tail's problem:	The dog's problem:
Unmeasured baseline covariates	Appropriate clinical assessments are either not performed or not recorded.
Residual confounding by indication	Reasons for treatment choices are not recorded – and may not be reasonable!
Informative censoring of outcomes	“Lost to follow-up” is too often the norm.

Our goal is to place systematic measurement at the center of health care quality. Research is just a side effect.

Residual confounding: We wouldn't need randomization to control for bias if we knew:

- What data did the provider consider when choosing a treatment?
- What logic did s/he apply?
- What exact choice did s/he make?

And shouldn't we know those things anyway?

Our role in improving data quality:

- Know that we are just the tail.
- Engage with health systems around measurement as a core function of care.
- Clearly identify measures suitable for health care delivery and research (e.g. PROMIS).
- Embrace new communication technologies.
- How can we capture (and improve!) the decision-making process?

When we say “sharing data”, do patients and providers see...

Isaiah's Peaceable Kingdom...



...or Orwell's Big Brother?



Reasonable questions patients ask:

- Can I know who is watching me?
- Can I know what those people are thinking or deciding about me?
- How will I now know how that my information helped other patients?

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Our traditional answer: Just trust us. You couldn't possibly understand it anyway.

For health care providers and systems

- “Coopetition” is a new game, and we’re still figuring out the rules.
- Transparency is a big leap down to the water. Who will jump first?

Safety in numbers is paradoxical:

- For patients: Mixing my data with everyone else may protect me, but it means I can't know what you're doing with my information.
- For health systems: A federated or distributed structure gives me control. But it means my results will distinguishable / identifiable.

Common Rule requirements:

- Exempt from IRB review if:
 - “the information is recorded by the investigator in such a manner that subjects cannot be identified”
- Informed consent can be waived or modified if:
 - “no more than minimal risk”
 - “will not adversely affect rights and welfare”
 - “research could not practicably be carried out without the waiver or alteration”

These are not insurmountable barriers.

Criteria/process for exemption may be relaxed by proposed new rules.
It gets stickier when we would assign or alter treatments.

Our role in transparency and trust:

- Clearly distinguish between patients' privacy rights and others' proprietary interests (i.e. lose the "HIPAA smokescreen")
- Tools for downstream transparency and upstream privacy

To be blunt, our current business model is about:

- Secrecy – If we have a really good idea, let's make sure no one finds out til we're finished.
 - Stasis – Let's be careful not to answer the question too quickly.
 - Inefficiency – How can we maximize grant revenue received per unit of learning?
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What if?

- Every NIH grant application were public as soon as it's submitted?
- Research results were available to other researchers, research participants, and the general public as soon as they are created?
- A new “impact score” for continued funding: How quickly were your ideas stolen?

Privacy protection for whom?

Patients



Providers and health systems



Researchers



Two fears about open access to big data:

- Threats to patient privacy from backwards identification
- Threats to scientific integrity from “data dredging”

Traditional solution:

- Limit access to those we trust (i.e. people like me)
 - Limit questions to those we accept (or agree with)
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An alternative security solution:

Anyone can ask any question at any time.

But –

- All questioners are identified
 - All questions and answers are public
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