We are never getting to precision medicine in psychiatry

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This treatment works 40% of the time on average!

How about one that works 100% of the time on me?
Lenze Disclosure of Interest

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Overview of today’s talk

RCTs

- Sample population
  - Group 1
  - Group 2

Precision Clinical Trials

New methods

design flaws in RCTs

biomarkers

I feel tired.
On a scale of 0 (not at all) to 100 (very much so).
This is a day in my life as a psychiatrist

**Depression:** “I’m on an antidepressant but I still feel depressed. What do I do now?”

**Anxiety:** “When I get worrying, it is hard to stop.”

**Cognitive problems:** “I’m having a lot of trouble with my memory. What can I do about it?”
Randomized controlled trials (RCTs) are a powerful tool for evidence-based medicine.

“New treatment is effective!”

- **Sample population**
- **Group 1**
  - **New treatment**
  - **Outcome**
- **Group 2**
  - **Control treatment**
  - **Outcome**

**Response rate**

- **50%**
- **40%**
- **30%**
- **20%**
- **10%**
- **0%**

**New treatment**

**Control**
Depression: “I’m on an antidepressant but I still feel depressed. What do I do now?”

Clinical trials provide answers!
Anxiety: “When I get worrying, it is hard to stop.”

Escitalopram for Older Adults With Generalized Anxiety Disorder
A Randomized Controlled Trial

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Context: Generalized anxiety disorder (GAD) is one of the most common psychiatric disorders in older adults; however, few data exist to guide clinicians in efficacious and safe treatment. Selective serotonin reuptake inhibitors (SSRIs) are efficacious for younger adults with GAD, but benefits and risks may be different in older adults.

Objective: To examine the efficacy, safety, and tolerability of the SSRI escitalopram in older adults with GAD.

Design, Setting, and Participants: A randomized controlled trial in primary care practices and related specialty clinics in Pittsburgh, Pennsylvania, of 177 participants aged 60 years or older with a principal diagnosis of GAD randomized to receive either escitalopram or placebo and conducted between January 2005 and January 2008.

Interventions: Twelve weeks of 10 to 20 mg/d of escitalopram (n=85) or matching placebo (n=92).

Main Outcome Measures: Cumulative response defined by Clinical Global Impressions—Improvement score of much or very much improved; time to response; and anxiety and role functioning changes measured by the Clinical Global Impressions—Improvement scale, Hamilton Anxiety Rating Scale, Penn State Worry Questionnaire, Late-Life Function and Disability Instrument—adult; limitations scale; and the role—emotional impairment and

Antidepressant Medication Augmented With Cognitive-Behavioral Therapy for Generalized Anxiety Disorder in Older Adults

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Objective: Generalized anxiety disorder is common among older adults and leads to diminished health and cognitive functioning. Although antidepressant medications are efficacious, many elderly individuals require augmentation treatment. Furthermore, little is known about maintenance strategies for older people. The authors examined whether sequenced treatment combining pharmacotherapy and cognitive-behavioral therapy (CBT) boosts response and prevents relapse in older adults with generalized anxiety disorder.

Method: Participants were individuals at least 60 years of age with generalized anxiety disorder (n=73) who were recruited from outpatient clinics at three weeks of maintenance escitalopram; escitalopram alone, followed by maintenance escitalopram; escitalopram plus CBT, followed by pill placebo; and escitalopram alone, followed by placebo.

Results: Escitalopram augmented with CBT increased response rates on the Penn State Worry Questionnaire but not on the Hamilton Anxiety Rating Scale compared with escitalopram alone. Both escitalopram and CBT prevented relapse compared with placebo.

Conclusions: This study demonstrates effective strategies for treatment of generalized anxiety disorder in older adults. The sequence of antidepressant medication augmented with CBT leads to worry
Cognitive training

Mindfulness training

Exercise

Cognitive problems:
“I’m having a lot of trouble with my memory. What can I do about it?”
In spite of evidence-based treatments, mental illness morbidity remains high.

<table>
<thead>
<tr>
<th>Illness category</th>
<th>Morbidity over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>↓↓</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>↓↓</td>
</tr>
<tr>
<td>Cancer</td>
<td>↓</td>
</tr>
<tr>
<td>Mental illness</td>
<td>😞</td>
</tr>
</tbody>
</table>

WHY?
Treatments work...

for some

[ Arif Khan et al, PLOS One 2012 ]
Psychiatry is “trial and error” medicine
Precision medicine = individually tailored treatments

Patient population

Standard approach

Tailored approach

Treatment

Treatment A (effective in 20% of target population; 80% is waste)

Treatment A
Treatment B
Treatment C
Treatment D
Precision medicine in psychiatry means markers as enrichment factors

- Genetic variants
- Neuroimaging
- Molecular tests
- Behavioral phenotyping
Precision medicine testing in RCTs

Sample population → Group 1 → Outcome
New treatment

Sample population → Group 2 → Outcome
Control treatment

Measure marker

“The difference of the differences”

Patients with factor
Patients without factor
There are 3 treatment-relevant subtypes in depression

- Bipolar subtype = Add mood stabilizer
- Psychotic subtype = Add antipsychotic
- Recurrent subtype = Maintain treatment
Flawed approach
First design flaw
We test biomarkers prior to treatment, not during treatment.
Second design flaw
We focus on giving a specified treatment exposure, not achieving a specified goal.
Third design flaw
We measure outcomes and predictors imprecisely

Measure response: “In the last 7 days, how has your mood been?”
Infrequent, retrospective measurement hurts sensitivity

What has your energy been for the past week?

Hmm....

Peak-End rule

We rate an experience by its peak or end... not by its sum.

[ Mofsen et al, JMIR Mental Health 2019 ]

[ Image 7x25 to 720x450 ]
Where’s the solution???
Precision Clinical Trials
RCTs should have **three** features in order to get our field to precision medicine:

1. **Adaptive treatment:**
   - individually adjust treatment
   - Goal is to optimize response

2. **Treatment-targeted enrichment:**
   - give acute bout of treatment
   - measure patient’s response

3. **Precise measurement:**
   - accurately measure outcomes
   - and predictor markers

[ Lenze et al, JAMA Psychiatry in press ]
Precision clinical trials: the easy part
Treatment targeted enrichment uses an acute phase of treatment to determine ultimate response.

- Measure response
- Symptoms or mechanism
Time out for a

Clinical Pearl

You took paroxetine before; how did that work for you?

Really well!

Let’s try paroxetine!
Acute treatment response predicts long-term outcome

Responders to open-label esketamine had better long-term outcome with maintenance esketamine compared to placebo

[ Daly et al, JAMA Psychiatry 2019 ]
A lead-in phase enriches the sample

Does adding vortioxetine help?

- Open lead-in Cognitive training only
  - Eligible & engaged: randomize
    - vortioxetine + cognitive training
    - placebo + cognitive training

[ Lenze et al, American Journal of Psychiatry, in press ]
Adaptive Treatment

Which is better, A or B?
Treatment should adapt to patient needs and preferences

- Call from therapist
- Prompt me to exercise
- Information on how to reduce my stress
- Provide an audio meditation

Example from Ginger Nicol
Precise measurement

What has your energy been for the past week?

Hmm....

Which is better?

or...

I feel tired.

On a scale of 0 (not at all) to 100 (very much so).

Drag to select

Not at all     Very much so

NEXT

[Mofsen et al, JMIR Mental Health, 2019; Moore et al, J Psych Res 2016]
High-frequency smartphone assessments can measure outcomes with high precision

Mindful MyWay study

Testing Commitment
This study has 3 parts and lasts a total of 18 weeks.

Part 1 (4 weeks)
You will be reminded 4 times a day to complete tests within the app.

Part 2 (10 weeks)
You will take one 45 minute mindfulness class a week and answer a few questions about your mindfulness practice twice a day.

Part 3 (4 weeks)
You will be reminded to complete tests 4 times a day, as well as a mindfulness survey once a day.

App created by happyMedium | healthyMedium;
Burst Cognitive Sampling created by Jason Hassenstab
Getting to precision medicine: the easy part

- Include an acute lead-in phase
- Adjust treatment to meet needs of individual
- Measure precisely

Sample population

Group 1
New treatment → Outcome

Group 2
Control treatment → Outcome
Precision clinical trials: new methods and tools
How brief can an acute lead-in phase be?

- Measure response
- Symptoms or mechanism
New tools will help us determine response to a brief bout of treatment – even a single dose.

**Precision TMS:**
Research rounds by Rita Haddad MD
Wednesday Feb 5, 11:30-12:45
Clopton Auditorium
mHealth interventions will combine smartphones and machine learning
A treatment could continuously *self*-adapt to the individual patient

[ Salehie et al, 2009 ]
New statistical methods can capture individual-level temporal dynamics

4 weeks’ data from an older adult with MDD

sad mood

thoughts of death

[ Piccirillo & Rodebaugh, Clin Psycholol Review 2019 ]
The mHealth Research Core is a new service for researchers

https://mhealth.wustl.edu/

Overview

Mobile Health (mHealth) research is focused on the use of social media, smartphone devices, tablets, web sites, sensors, wearables and/or other remote technology to measure and improve health research and outcomes.

mHealth is widespread and understudied relative to its importance and potential.

To foster collaboration at WUSTL, the Institute for Clinical and Translational Sciences (ICTS) recently established the mHealth Research Core, in partnership with the Institute for Informatics (II), the HealthCare Innovation Lab and the Healthy Mind Lab.

Next meeting Wednesday March 11 10-11:30am, Schwarz auditorium
Changing the culture will be the hardest part.

Conduct large RCTs → Convince funders → Change practice → Convince regulators → Conduct large RCTs
What will psychiatric treatment be like if we succeed?