Disruptive Innovations in Clinical Neuroscience: Where will we find the next generation of therapeutics?

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[Disclosures - None]

Treatment has increased over past decade

A. Antidepressant prescriptions
B. Antipsychotic prescriptions

(millions of prescriptions in US market – IMS Health)
Psychotropic medications are prescribed widely

Top therapeutic classes by spending (2011)
(billion $s of sales in U.S. market – IMS Health)

Sales measured in $billions
1. Lipitor  7.7
2. Plavix  6.8
3. Nexium  6.2
4. Abilify  5.2
5. Advair Diskus  4.6
6. Seroquel  4.6
7. Singularair  4.6
8. Crestor  4.4
9. Cymbalta  3.7
10. Humira  3.5

IMS Health
Top line market data
Inconvenient Truth #1: High Morbidity

**Causes of Disability by Illness Category**

*Global (ages 15-49)*

- Mental & behavioral disorders
- Musculoskeletal disorders
- Other non communicable
- Neurological disorders
- Chronic respiratory disease
- Diabetes/urogen/blood/endocrine
- Transport injuries
- HIV/AIDS & tuberculosis
- Cardio & circulatory disease
- Digestive diseases
- Cancer

Source: WHO World Health Report 2010

Inconvenient Truth #2: High Mortality

- Over 37,000 suicides per year in the U.S. (2010; CDC)
  - 90% related to mental illness (Mann, 2002)
- For context:
  - 17,000 homicides (2009; NCHS)
  - 34,000 traffic fatalities (2010; NTSB)
  - < 20,000 AIDS deaths (2009, CDC)

**Life expectancy w schizophrenia: 15 fewer years male, 13 fewer years female**

(cardiopulmonary, metabolic, multiple conditions)

(Crump et al., Am J Psych, 2013)
MORTALITY FROM MEDICAL CAUSES

The Therapeutic Paradox

Increased treatment as measured by epidemiology, prescriptions, expense
No decrease and, in some areas, increase in morbidity and mortality
Explanations:
Effective treatments, but prevalence is increasing
Effective treatments, but delivery is inadequate
Current treatments are not effective enough to influence public health outcomes
How do we get better therapeutics?

Disruptive Innovations in:
- New molecular targets
- New clinical targets
- New culture of clinical neuroscience

Transforming Treatment Development

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- 6 years
- Success rate < 1%
- 6 years
- Success rate < 10%
- Total cost roughly $2B
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Molecular targets for mental disorders?

For heritable disorders (autism, bipolar, schizophrenia): too many not too few (> 100)
- Schiz/BP: TCF4, CACNA1, KCNH2, VIPR2, DISC1, ANK3, miR-137
- Autism: NLG3, NiG4, Shank 3, Shank 2, Neurexin 1, CNTNAP-2, SCN2a

Implicate ion channels, synaptic pathways, neurodevelopmental genes (not monoamines)

For less heritable disorders (MDD, PTSD):
- Expression studies implicate trophic factors (FGF2, BDNF), epigenetic factors (HDAC-2), transcription or other factors (MIF, neuritin, P11) - not 5HT, NE, DA
Getting from genomics to molecular targets

Genomic association (GWAS finding, CNV, mutation) ≠ molecular target

Most compelling targets (BCL11a, PCSK9, Nav1) are involved in pathophysiology

Protective alleles may be better as druggable targets

Somatic mutations have provided some of the best targets

Need to focus clinical trials on target validation

Transforming Treatment Development

Move quickly into humans (pre-clinical is not predictive)
Drug is a probe of target (is target engaged? dose?)
Target validation is goal (does target change disease?)
Fast fail is success (increase Phase 3 success)
New Kinds of Targets?

A jump-start for electroceuticals

How do we get better therapeutics?

Disruptive Innovations in:

New molecular targets
New clinical targets
New culture of clinical neuroscience
CF due to one of >1500 different mutations in the same gene
G551D mutation results in full protein that does not function.
Ivacaftor (Kalydeco) approved by FDA in January, 2012.
Only 4% of CF patients have this mutation.
Precision Medicine for depression

“Depression”
Memory bias
Attention bias
Emotional appraisal bias
Amotivational states
Anhedonia
Deficit in self esteem
Social anxiety
Suicidal thoughts
Psychomotor retardation

Cognition and Behavior

New Clinical Targets for Mental Disorders

Insel, Sci Transl Med, 2012

Rapidly acting antidepressants
Ketamine, NR2b antagonist, Muscarinic antagonists

Prosocial compounds
GABA-B agonists (Arbaclofen), mGluR5 antag, OT/AVP

Cognitive enhancers for deficits in exec. fcns
GlyT inh, Alpha-7 nicotinic agonists, H3 antag, AMPA PAMs
Transforming Treatment Development

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Target Validation

Expt’l Medicine

Repurposing

Astute clinical observation
Stratified patient groups
Adaptive designs

How do we get better therapeutics?

Disruptive Innovations in:
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“New directions in science are launched by new tools much more often than by new concepts. The effect of a concept-driven revolution is to explain old things in new ways. The effect of a tool-driven revolution is to discover new things that have to be explained.”


New Tools Will Yield New Targets!

Protective LOF mutations, Pathway targets, epigenetics

Cell replacement Rx, Plasticity agents

Circuit based Rx, rTMS, DBS

Cognitive training

mHealth, Social networks

*Beyond magic bullets: true innovation in health care*

Valstar A. Tamagno, Marco Mielewiczki, Gary Pisano, Michael Ilag and Hossain K. Mirza

The time has come to move beyond product-focused “magic bullet” therapeutic development strategies towards models that can also incorporate devices, tools and services to provide integrated health-care solutions.
New Opportunities for Therapeutics

Revolutionary neuroscience:

Epigenetics
New molecular targets
Rapid treatments
Circuit-based Rx
Cognitive training
Devices
Combined interventions

Transforming Translation:

Precompetitive partnerships
Experimental medicine
Precision medicine
Network solutions
Patient centered care

Transforming the Culture for New Therapeutics

Academia
Innovative Medicines Initiative (EU-AIMS, NewMeds)
Foundation for NIH (Biomarkers Consortium)
Critical Path Institute (c-DISC, CAMD)
Sage Bionetworks (CommonMind)
One Mind for Brain Research
Trans-celerate
Arch2POCM

Foundations

Industry

Government
How do we get better therapeutics?

Disruptive Innovations in:
New molecular targets
(From Monoamines to Genomics, Systems Neurosci)
New clinical targets
(From DSM to RDoC, Repurposing)
New culture of clinical neuroscience
(New tools, standards, sharing, integration)
From Neuroscience to Mental Health: A Vision for the 21st Century

Dissemination Access Coordination Translating Research to Practice

NIMH
National Institute of Mental Health
Paving the Way for Prevention, Recovery, and Cure
www.nimh.nih.gov

Preventive interventions
Molecular diagnostics
Proteomics
Neuroimaging
Clinical genomics

Pathophysiology

Next-Gen Clin Trials
Exptl Medicine
RDoC
Biodiagnostics
Treatment of core pathology
Personalized care

Genes Cells Systems Individual Social

Diagnosis by symptoms Treatment of episode

Strategic prevention Recovery and Cure