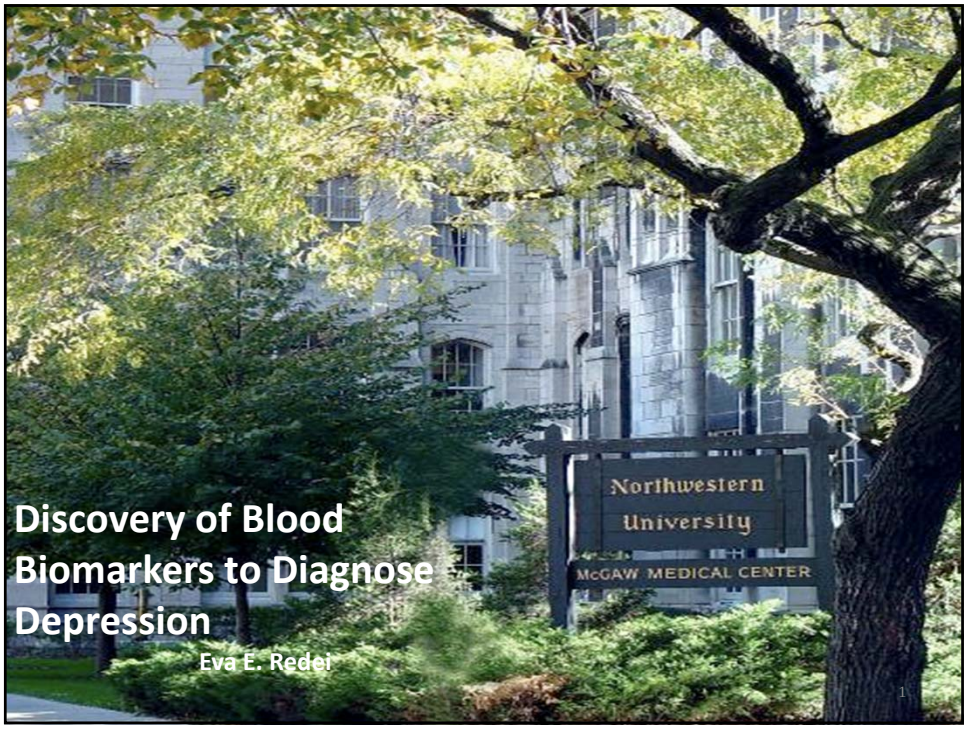

Discovery of Blood Biomarkers to Diagnose Depression

Eva E. Redei

1

Outline

- **What is depression?**
  - **–Definition throughout history**
  - **– Alarming statistics**
- **Who is vulnerable?**
- **How is it diagnosed?**
  - **– Why do we need laboratory diagnostic tests?**
  - **– Multi-marker panel to diagnose MDD, subtypes, predict treatment outcomes, and aid in discovery of novel antidepressants**

Eva E. Redei 2012 2

Depression

"...every ray of hope destroyed and not a wish to gild the gloom"

-Robert Burns (1759-1796)

Depression throughout History

- **Hippocrates** (c. 460 BC - 370 BC) of Ancient Greece: Imbalance of the humors
  - Melancholia from *melas* (black) and *khloe* (bile)
- **Galen** (129 AD – c. 200 AD) of Pergamon (Turkey): sadness, dejection, despondency often fear anger, delusions and obsessions
- **Avicenna** (c. 980 AD– 1037 AD) Persian: described melancholia similarly to our current definition of depressive type of mood disorder.

Depression throughout History

- **Robert Burton** (1599-1640): "The Anatomy of Melancholy". "This *Melancholy* of which we are to treat, is a habit, a serious ailment, a settled humour…not errant, but fixed: and as it was long increasing…, it will hardly be removed".
- **Emil Krapelin** (1856-1926): origin of psychiatric disease to be biological and genetic malfunction.
- **Henry Maudsley** (1835-1918): Influenced Darwin proposed the term affective disorder.
- **Charles Darwin** (1809-1882): "The expression of the emotions in man and animals". Genetically determined aspects of behavior.

Depression throughout History

- **Sigmund Freud** (1856-1939): Founder of psychoanalysis. Melancholia could result from mourning for an objective loss and of a subjective one when the individual's ego is compromised.
- **Currently**:
  - Depression is either endogenous (melancholic) considering a biological condition, or reactive (neurotic) a reaction to a stressful events, and/or
  - depression is caused by a chemical imbalance in neurotransmitters in the brain.

Depression Categories

Unipolar

- **Major Depressive Disorder (MDD):** One or more major depressive episodes
- **Dysthymia**: Depressed mood for most days during the past two years
- **Depressive disorder not otherwise specified:** Depressive symptoms do not fit neatly in the *DSM-IV* criteria for the other disorders

Bipolar

- **Bipolar type I**: One or more manic episodes; often accompanied by depressive episodes
- **Bipolar type II**: One or more hypomanic episodes and at least one major depressive episode
- **Cyclothymia**: Two-year period of cycling hypomanic symptoms and depressive symptoms that fail to meet DSM-IV criteria for MDD
- **Mixed state:** Meet criteria for both manic episode and major depressive episode almost every day for at least one week

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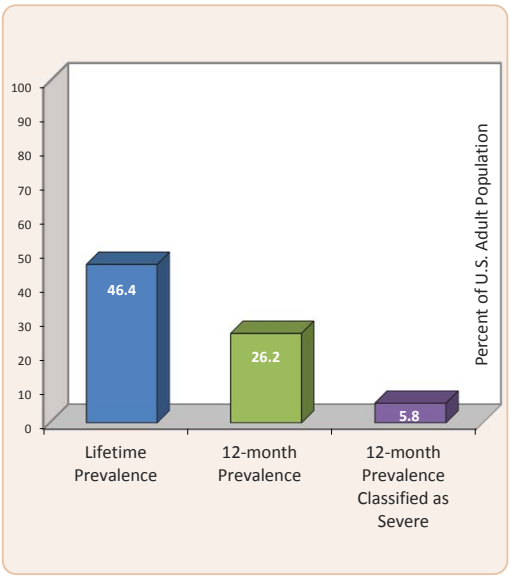
Any Mental Disorder Among Adults



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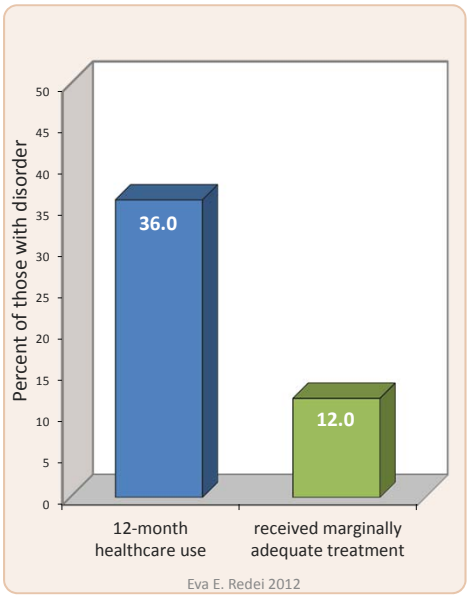
NIMH STATISTICS

Treatment for Any Mental Disorder



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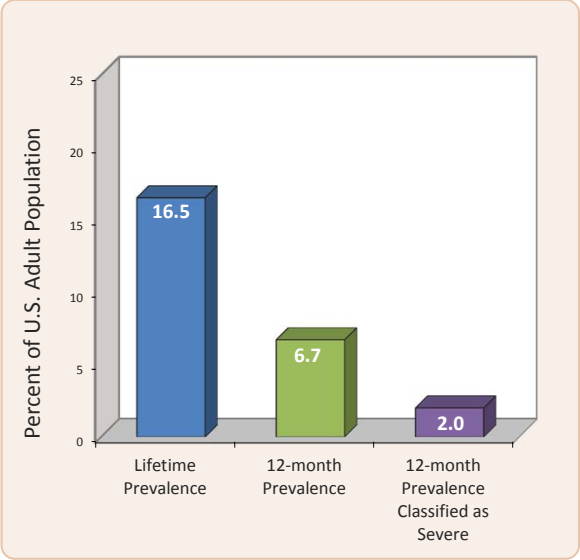
NIMH STATISTICS

Major Depression in Adults



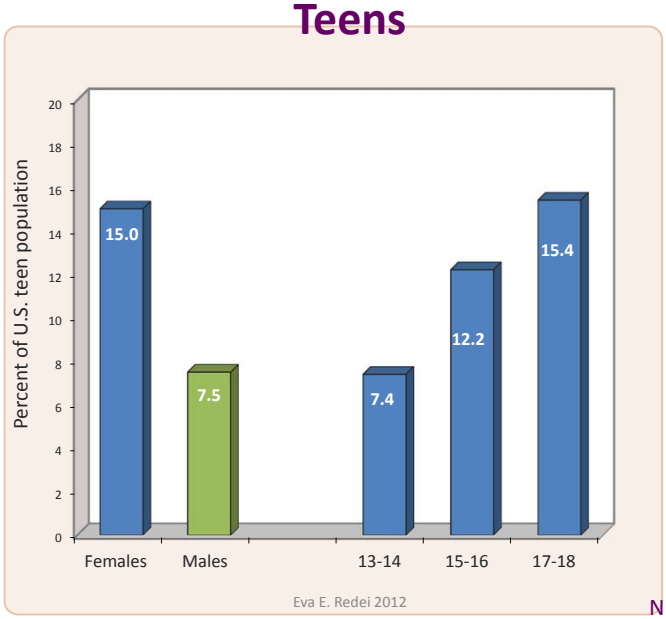
Recurrence rates are over **50** percent after the first depressive episode; **70** percent with two episodes; and over **90** percent with three or more episodes.

NIMH STATISTICS

DEMOGRAPHICS

- **Sex**: Women are 70% more likely than men to experience depression during their lifetime
- **Race**: Non-Hispanic blacks are 40% less likely than non-Hispanic whites to experience depression during their lifetime
- **Age:** Compared to adults over the age of 60
  - 18-29 year olds are 70% more likely during lifetime, but 200% more for 12 month prevalence
  - 30-44 year olds 120% more likely during lifetime, and 80% more for 12 month prevalence

12 month Prevalence of Major Depression in Teens



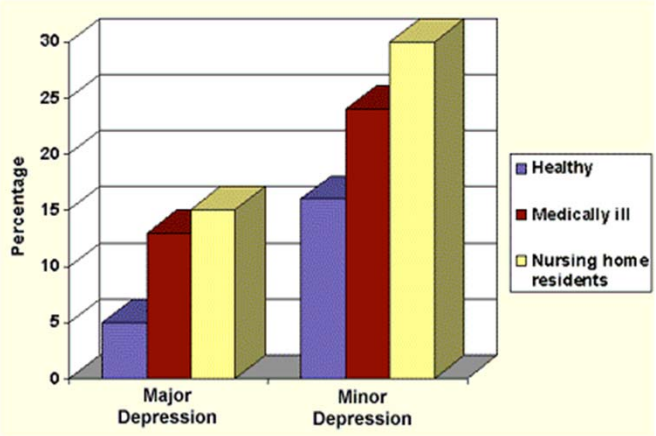
Eva E. Redei 2012

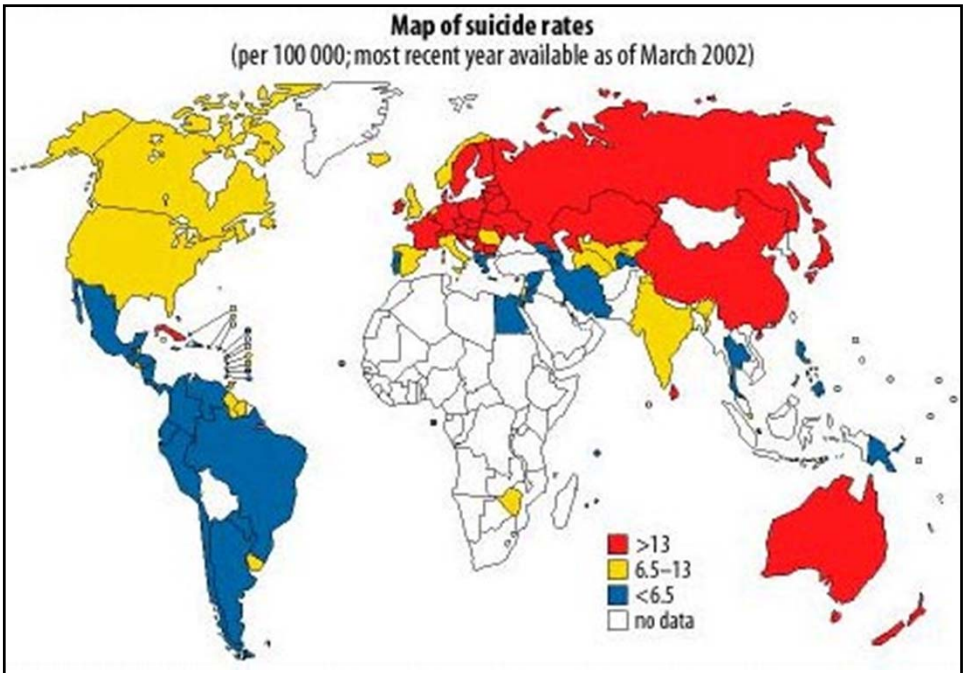
NIMH STATISTICS

Postpartum Depression

- Occurs in 15-20% of adult women; 26-32% of adolescents
- Symptoms peak at 3-6 months
- Can become chronic

Late-Life Depression

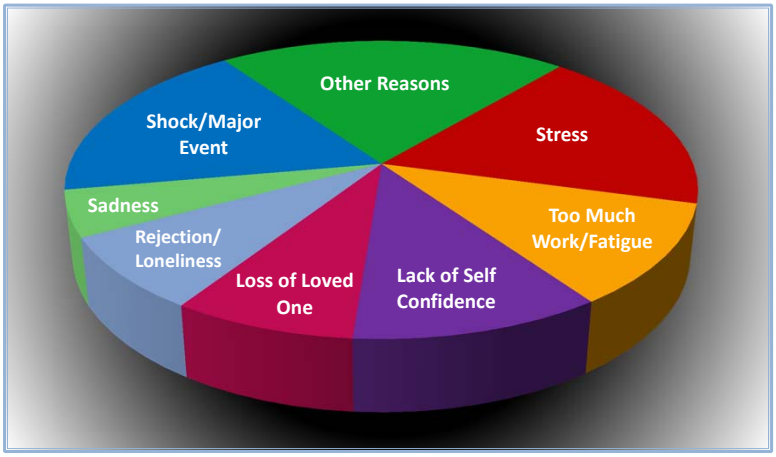




Outline

- What is depression?
  - Definition throughout history
  - Alarming statistics
- **Who is vulnerable? Etiology?**
- How is it diagnosed?
  - Why do we need laboratory diagnostic tests?
  - Multi-marker panel to diagnose MDD, subtypes, predict treatment outcomes, and aid in discovery of novel antidepressants

In your opinion, what causes depression?



Etiology

1. **Genetic predisposition**
   - Major Depressive Disorder aggregates in families, vulnerability is affected by a **large number of genes.**
2. **Internal Environment**
   - **Hormonal environment**
3. **External Environment**
   - **Early life stress, abuse, loss**
   - **Stress, trauma, loss before the onset of depression**

BUT, also many chronic diseases:
Parkinson's
Alzheimer's
Cardiovascular diseases
Chronic autoimmune diseases: lupus, MS, and many more

Why Study Genetic Predisposition?

- The neurobiological basis of individual differences
- The etiology of diseases that should lead to the discovery of new and more specific drug treatments
- The treatment response differences: DNA testing will be used to predict which patients will respond to specific drugs or be susceptible to particular side effects

YESTERDAY:
HUMAN GENOME PROJECT

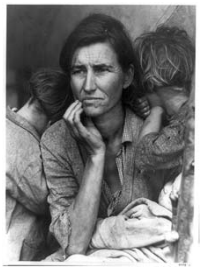
TODAY

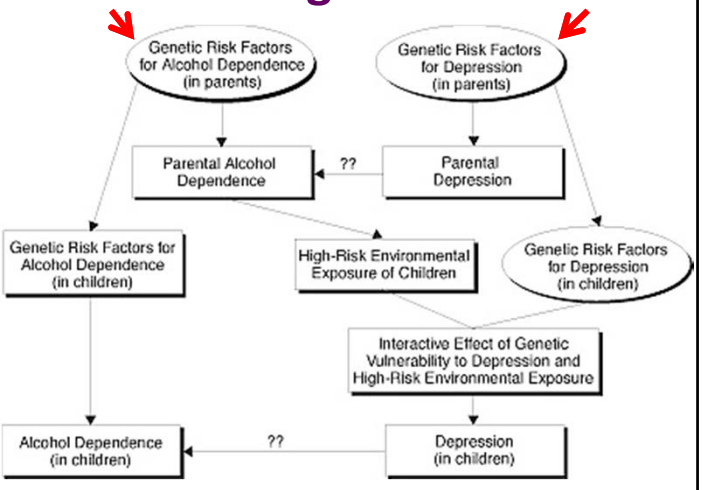
Ion Proton DNA Sequencer Decodes a Human Genome in One Day for $1,000

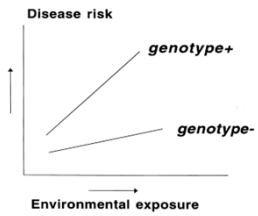
Hormonal changes elicit depression

- **P**remenstrual **D**ysphoric **D**isorder **– Rising levels of Estrogen**
- **P**ostpartum **D**epression **– Declining levels of Estrogen**
- **P**erimenopausal **D**epression **– Declining levels of Estrogen**
- Hypothyroidism **– Low levels of Thyroid Hormones**
- Cushing Disease/Syndrome **– High levels of Cortisol**
- Diabetes **– High levels of Glucose; low Insulin**
- Aging – **Low levels of Testosterone**

Early life stress and genetics







Heath & Nelson, 2003

Stress, trauma, loss before the onset of depression

1. Episodes of depression are often associated with stressful life events
2. Chronic stress leads to elevated morning cortisol levels, similar to melancholic depressed patients
3. Stress and depression have similar consequences manifested in increased prevalence or worsened presentation of various illnesses

Stress and depression have similar consequences manifested in increased prevalence or worsened presentation of various illnesses

Alcoholism, Drug Abuse
Coronary Heart Disease
Hypertension
Anxiety Disorders
Ulcerative Colitis
Obesity
Type II Diabetes
Asthma
Crohn's Disease
Systemic Lupus Erythematosus
Multiple Sclerosis

and many more……

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Diagnosis

- "The diagnosis of mental disorders must rest with the **patients' reports of the intensity and duration of symptoms, signs from their mental status examination**, and **clinician observation of their behavior including functional impairment**.
- These clues are grouped together by the clinician into recognizable patterns known as syndromes. When the syndrome meets all the criteria for a diagnosis, it constitutes a mental disorder."

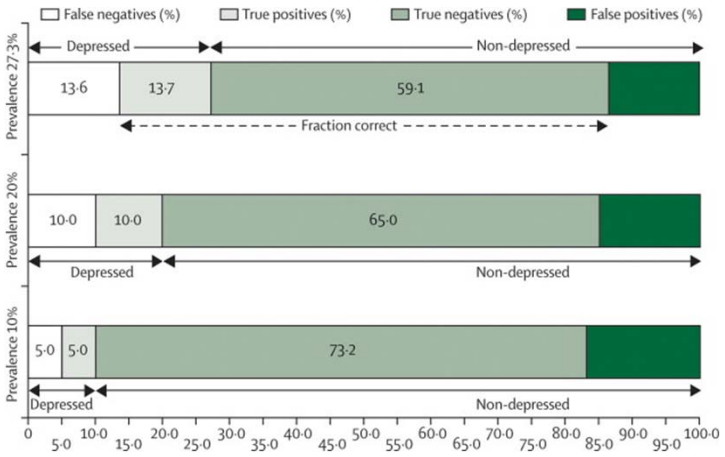
Mental Health, The report of the Surgeon General

Major Depressive Disorder: Diagnostic Criteria

At least five of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure.

1. depressed mood most of the day, nearly every day
2. markedly diminished interest or pleasure in all, or almost all, activities
3. significant weight loss or weight gain when not dieting
4. insomnia or hypersomnia nearly every day
5. psychomotor agitation or retardation nearly every day
6. fatigue or loss of energy nearly every day
7. feelings of worthlessness or excessive or inappropriate guilt
8. diminished ability to think or concentrate, or indecisiveness
9. recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Clinical diagnosis of depression in primary care: a meta-analysis (N=50,371)



Alex Mitchell, et al.. The Lancet. 2009

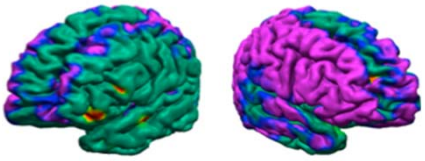
Diagnosis

The diagnosis of mental disorders is more difficult than diagnosis of somatic, or general medical, disorders, since there is no

- definitive lesion,
- *abnormality in brain tissue that can identify the illness*, or
- *laboratory test*

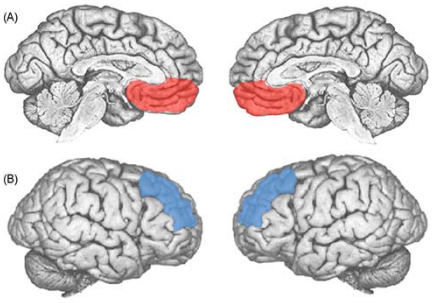
Mental Health, The report of the Surgeon General

Anatomical Markers of Depression



MRI brain maps of differences in tissue thickness between high- vs. low-risk for familial depression. Blue and purple denote thinner areas in the high-risk group; yellow, orange, and red are significantly thicker areas; green areas show little to no difference in tissue thickness.

Myrna Weissman, 2009



Regional blood flow and/or glucose metabolism. (A) **Ventromedial frontal cortex** is hyperactive, while (B) **Dorsolateral frontal cortex** is hypoactive in depression.

Koenig and Grafman, 2009

Molecular Biomarkers

- **Trait: Independent of disease state; genetic markers of susceptibility (DNA)**
- **State: Changes by disease state, BUT changes occur in the brain!**
  - Gene expression markers of disease states **(RNA)**
  - Protein markers of disease states **(Protein)**

The stigma of depression and the lack of biological markers

- Most mental health conditions are referred to as disorders, rather than as diseases, because diagnosis rests on clinical criteria. **The term "disease" generally is reserved for conditions with known pathology or detectable physical change.**
- The term "disorder," on the other hand, is reserved for clusters of symptoms and signs associated with distress and disability (i.e., impairment of functioning), **yet whose pathology and etiology are unknown and no physical change can be detected**.

Mental Health, The report of the Surgeon General

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What are the most urgent tasks

- Objective laboratory diagnosis for different types of depression
- Individualized treatments based on exact, objective diagnosis and individual vulnerabilities (genetic or environmental)
- Development of antidepressants with novel mechanism of action; closer to etiologies

- **ACKNOWLEDGE THAT DEPRESSION IS A DISEASE LIKE ANY OTHER DISEASE – IT NEEDS TO BE CURED!!!!**

NEW YORK TIMES MAGAZINE

32 Innovations That Will Change Your Tomorrow

Translational Psychiatry (2012)
Published online 17 April 2012

Discovery of blood transcriptomic markers for depression in animal models and pilot validation in subjects with early-onset major depression

K Pajer[1,5], B M Andrus[2,5], W Gardner[1,3], A Lourie[3], B Strange[3], J Campo[3], J Bridge[3], K Blizinsky[2], K Dennis[2], P Vedell[4], G A Churchill[4] and E E Redei[2,5]

Blood test looks promising in diagnosing depression
A preliminary study finds certain biological markers in the blood of teens with depression that are absent in healthy counterparts. It could lead to the first diagnostic testing for depression.
Los Angeles Times

Teen Depression Can Be Diagnosed With New Blood Test, Northwestern University Says
Huffington Post

Scientists develop first blood test to diagnose depression
FoxNews.com

Depression in Teens Could Be Diagnosed with Blood Test
A blood test based on 11 genetic markers could make early-onset diagnosis easier and possibly relieve the stigma of depression
Scientific American

AND
NBC, WebMD, ABC,CBS, CNN, WGN, WTTW, Voice of America, AMA, NPR, The Daily Beast, Health Day, The New Scientist, Boston Globe, BBC, over 700 articles……

Novel Approach

- **Identified candidate blood markers from two animal models:**
  - **Genetic model of depression**
  - **Chronic stress model of depression**
- **"Translated" putative blood markers to human**
- **Test these blood markers in human subjects with major depression, starting with teens.**

Unique Genetic Animal Model of MDD

- **Mirrors at least five of MDD diagnostic criteria**
- **Control strain genetically close, but not impaired**
- **We selectively bred Wistar Kyoto rats, strain well-known for depressive characteristics**
- **Animals on the extremes of depressive behavioral tests selected for breeding; sibling mating avoided until G5 generation. Currently at 26-27th generation.**

Pajer et al., Translational Psychiatry, 2012

Transcriptomics of Genetic Model of MDD

- Genome-wide gene expression analyses of **blood, frontal cortex, amygdale, hippocampus, and striatum** of the depressed (WMI) and non-depressed strains (WLI)
- 11 candidate transcripts showing significant, and same-directional expression differences in **blood and one or more of the brain regions** between the two strains

Pajer et al., Translational Psychiatry, 2012

Chronic Stress Animal Model of MDD

- Temporarily mirrors at least five of MDD diagnostic criteria
- Genetically distinct strains of rats exposed to prolonged, repeated psychological stress for 14 days.
- Genome-wide gene expression analyses of blood of chronically stressed (CRS) and not-stressed (NS) groups.
- 15 transcripts with significant differences between CRS and NS groups selected as chronic stress markers.

Pajer et al., Translational Psychiatry, 2012

MDD vs. No Disorder

- MDD = 14, No Disorder = 14
  - MDD group: 8 girls & 5 boys; mean age 16.6 years
  - No Disorder group: 12 girls & 2 boys; mean age 16.3 years
- A panel of 11 blood markers differentiated participants with early-onset MDD from the ND group
- The genes expressing these transcripts belong to three broad functional categories: those involved in transcription, neurodevelopment and neurodegeneration.

Pajer et al., Translational Psychiatry, 2012

MDD vs. MDD + Anxiety Disorder

- MDD = 5, MDD + Anxiety = 9
- A non-overlapping panel of 12 transcripts distinguished subjects with MDD alone from those with comorbid anxiety.

Pajer et al., Translational Psychiatry, 2012

Early Stress Markers

- MDD = 9, No Disorder = 8
  - MDD group: 6 girls & 3 boys; mean age 16.8 years
  - No Disorder group: 7 girls & 1 boys; mean age 16.4 years
- Four transcripts, originating from the chronic stress animal model, significantly correlated with maltreatment scores in youths

Pajer et al., Translational Psychiatry, 2012

Criteria for a Successful Biological Diagnostic Test

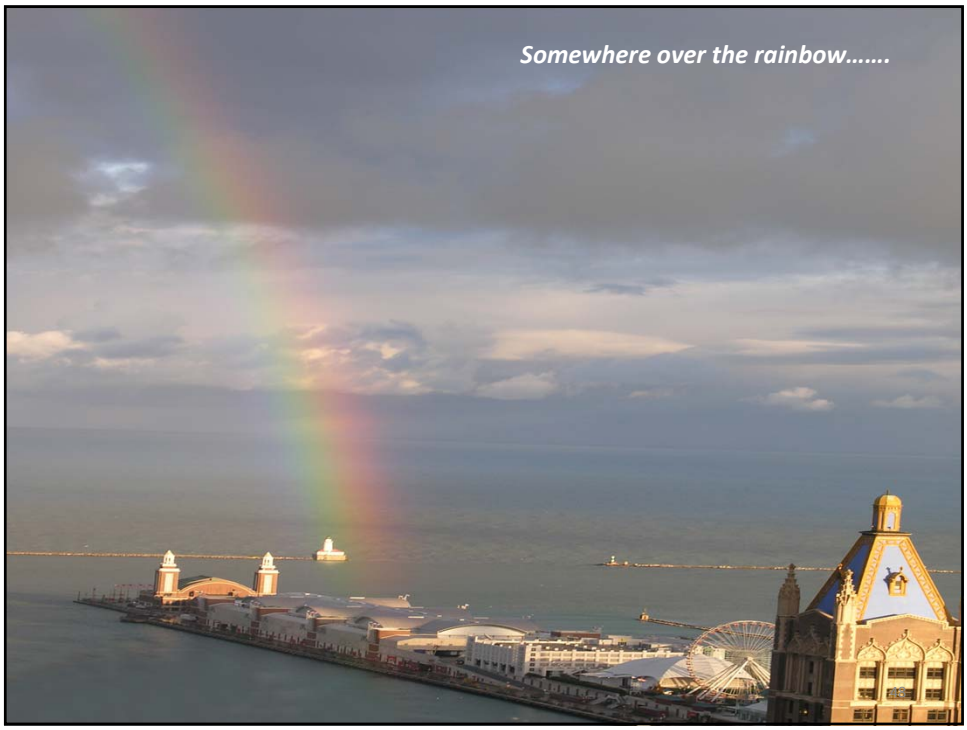
1. The disease should represent a substantial burden at the public health level and should have a prevalent, asymptomatic phase. ✔
2. The asymptomatic phase should be recognizable. ✔
3. The diagnostic test should have reasonable sensitivity ?, specificity ?, be of low risk and low cost ✔, and be acceptable to the patients and the physicians both.
4. Curative potential should be substantially better in early compared with advanced stages of disease. ✔
5. Treatment of patients whose disease is detected by the diagnostic test should decrease cause-specific mortality, morbidity and/or disease burden. Likely

Next Steps

- **For validity:**
  Large study of MDD with and without anxiety
- **For specificity:**
  Larger study with MDD and other psychiatric disorders
- **Diagnostic array**

One day we will

- Diagnose subtypes of depression
- Know when to give antidepressants and what kind
- Develop novel antidepressants
- **Eliminate stigma by knowledge**



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Special thanks to Bill Pare!!

Outline

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CURRENT ANTIDEPRESSANTS: History of Monoamine Deficiency Hypothesis

- 1951, Irving Selikoff and Edward Robitzek: patients treated with new anti-tuberculosis agents, ***isoniazid*** and ***iproniazid*** " exhibited renewed vigor"
- 1952, Delay and Buisson; 1953, Lurie and Salzer; ***isoniazid*** improved depression in two thirds of their patients. The mode of antidepressant action of ***isoniazid*** is still unclear. ***Ipronazid*** proved to be a potent monoamine oxidase inhibitor.
- 1957, a compound that Kunh generated to improve the efficacy of chlorpromazine became imipramine, the first tricyclic antidepressant, that were shown by the 1960s to inhibit norepinephrine reuptake.
- 1965, Joseph Schildkraut to publish his paper called **"The Catecholamine Hypothesis of Affective Disorders"**
- 1969-1987 researchers modified antihistamine-derived compounds to target the serotonin system resulting in the first SSRI, ***fluoxetine***.

1980 to 2000
SSRIs and SNRIs
After the development of Prozac, modern antidepressants flooded the market.

1987

Fluoxetine (Prozac)

Prozac is the first SSRI antidepressant developed. It's introduction to the market is hailed as a miracle drug for treating depression because it has fewer side effects than the previous drugs.

1991 to 1998

More SSRIs approved and SNRIs developed

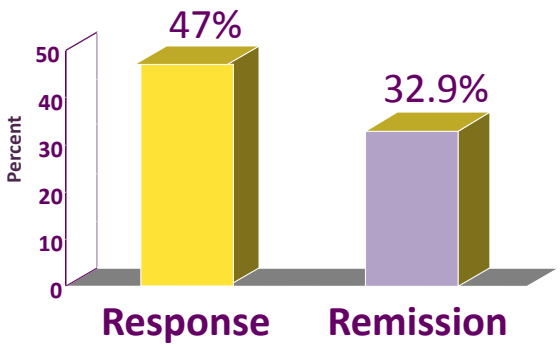
After the introduction of Prozac, many more SSRI medications followed. Additionally, new antidepressants are developed similar to SSRIs but that also target norepinephrine as well (SNRIs).

SSRIs	SNRIs
1991 – sertraline (Zoloft)	1993 – venlafaxine (Effexor)
1992 – paroxetine (Paxil)	1994 – nefazodone (Serzone)
1998 – citalopram (Celexa)	

Thus, discovery of antidepressants led to the monoamine deficiency hypothesis of depression, and this led to more monoamine-related antidepressants….

Antidepressant efficacy: STAR*D:

- Major Depressive Disorder, ages 18-75, Clinical sample with other disorders
- Citalopram 20–60 mg 12-14 wks (n=2876)

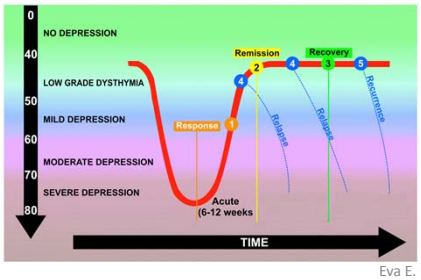


Trivedi MH et al. *Am J Psychiatry.* 2006;163:28

Recurrence of Major Depressive Episode

Recurrence is less for those who remitted fully

- **Remitted: 33.5%**
- **Responded but not remitted fully: 58.6%**



Rush et al, . *Am J Psychiatry*. 2006

Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition, Text Revision (DSM-IV-TR)

- **Specify depression as:**
  - Mild; Moderate; Severe without Psychotic Features; Severe with Psychotic Features
  - Single Episode/Recurrent
  - In Partial/Full Remission
  - Chronic
  - Melancholic/ Atypical
  - Postpartum Onset
  - Seasonal Affective Disorder, e.t.c.

BUT, antidepressant treatments are the same for most