

## Pharmageddon in Mental Health Care

*"Are we getting better?"*

Michael Palladini, RPh MBA

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## Objectives

- Participate in a critical analysis of the paradigm of care in mental healthcare, including short and long term outcomes
- Understand the history of the current model and the diagnostic criteria of disease.
- Become familiar with the medications utilized and the process of clinical trials and marketing, industry bias, economic and guild influence.

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## \$ Follow the Money \$




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"mostly mineral oil containing about one percent fatty oil (thought to have been beef fat), along with some red pepper (which would impart a soothing warmth to the skin) and possible traces of turpentine and camphor"

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- The \$395 billion US pharmaceutical industry spent \$5.2 billion on advertising prescription drugs directly to consumers in 2015.
- United States and New Zealand are the only two countries where direct-to-consumer (DTC) advertising of prescription drugs is legal.
- Prescription drugs accounted for 17% of total health care spending, up from 7% in the 1990s

Source: Nielsen




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**A good morning after a sleep-through night**

**Quaalude-300**  
(flunitrazepam tablets)

**A good morning after a sleep-through night**

**Quaalude-300**  
(flunitrazepam tablets)

*"Side effects reported have been mild, transient and have often proved to be statistically insignificant when compared to placebo effects"*

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**Introducing METADATE CD Capsules**

**One dose covers his ADHD for the whole school day**

**Designed to work when he needs it most**

**The hours mean, ask your doctor or call toll free 1-800-ADHD-INFO. Look for us on the World Wide Web at www.merck.com/cd-caps**

**IMPORTANT SAFETY INFORMATION FOR PATIENTS:**

**METADATE CD Capsules should not be used in children under 6 years of age.**

**Merck and Co., Inc. METADATE CD (methylphenidate HCl, USP) Extended Release Capsules, 10 mg**

•History was made and international law openly defied with the publication of this ad in magazines like Ladies' Home Journal, Parade and Redbook in 2001, the first time that a highly-addictive Schedule II controlled substance (methylphenidate) was advertised directly to the general public in flagrant violation of the United Nations Convention on Psychotropic Substances

•Resulted in a Cease and Desist letter from US DEA

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**Expanding Horizons in the New Century**  
10TH ANNUAL CONFERENCE ON ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Thank you to the following organizations for their generous grants

**CHADD**  
CHILDREN & ADULTS WITH  
ATTENTION-DEFICIT/  
HYPERACTIVITY DISORDER

**October is  
ADHD  
Awareness  
Month**  
CHADD.org

**PRESENTER'S CIRCLE**

**Shire**  
Medeva  
MALLINCKRODT  
Novartis

**PLATINUM LEVEL**  
NOVARTIS

**GOLD LEVEL**  
Lilly

**BRONZE LEVEL**  
Abbott Laboratories  
Pfizer, Inc.

**PATRON LEVEL**  
Schering-Plough  
Caplan, Inc.

**EXHIBIT HALL GRAND OPENING RECEPTION**  
Bentley Life Sciences  
Bentley Pharmacy School  
Bentley Learning Corporation

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**Psychodynamic Theory**




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**Diagnostic and Statistical Manual of  
Mental Disorders (DSM)**

- DSM I 1952 (106 "reactions")
- DSM II 1968 (182 disorders)
- DSM III 1980 (265 disorders)

\*Radical Revision: Symptom based, Criteria

- DSM IIIR 1987 (292 disorders)
- DSM IV 1994 (297 disorders)
- DSM-5 2013 (>300 disorders)

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## DSM 5

- Addition of a “Disclosure Policy” to add transparency.
- Eliminate bias
  - However, 69% report ties
  - FCOI issues
- Diagnoses use word “*often*” in criteria
- “False positive problem”
- There is not one biological marker/test included in the DSM

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## APA Guild

Control of:

- -Diagnosis of mental disorders
- -Research into their causes
- -Prescribing of psychiatric medications

3 distinct factions within APA in the 1970's (DSM III changed and united)

- -psychoanalysts
- -social psychiatrists
- -**biological orientation**

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## APA Guild

- 1981: Established “Division of Publications and Marketing”
  - “Advance the profession of psychiatry”
  - American Psychiatric Press, published texts, books and *American Journal of Psychiatry*
  - Establishment of a *Public Affairs Network* (1985)

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## APA Guild

- Mid-1980's, APA lobbied Congress to establish Oct 6-12 as "Mental Illness Awareness Week"
- Development of "Fact Sheets"
- Workshops for psychiatrists on "How to Survive a Television Interview"
- PSAs produced
- Published books such as *Psychiatric Illness: A Guide for the Family*; *1001 Questions About Psychiatry*; *Don't Panic*
- 1988 APA 5 year plan "Let's Talk About Mental Illness"
  - Expand speaker's bureau
  - newsletter
  - Educate public about anxiety and depression

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## Xanax (Upjohn) and Prozac (Lilly) influence

-3 public education films: (funding from Upjohn)

*Panic Prison* (1989)

*Faces of Anxiety* (1990)

*Depression: The Storm Within* (1991)

- 1992, Boots Pharmaceuticals sponsored workshops on depression, primarily taught means to reach PCPs and send a positive message about psychiatry.




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Early 1990s APA and National Mental Health Association (NMHA) create nationwide education campaign:

1. *Clinical depression is a medical illness*
2. *Effective treatments are available*
3. *See a doctor for help*

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- 1994 National Awareness Week included a "National Depression Screening Day"  
Theme: *"Treatment Works!"*  
65,000 people screened that week at 1,300 sites  
*"Let's Talk About Mental Illness Campaign"*
- Additional campaigns in the early 2000s:  
*"Healthy Minds, Health Lives"*  
*"Depression is Real"*  
*"Typical or Troubled" (for teens)*

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## Partnership

- APA grant from Pharmaceutical Industry:  
\$294 thousand in 1976 to \$1.36 million in 1980
- Advertising revenue increased, as part of total APA revenue increased:  
1980: \$10.5 million  
1990: \$24.9 million  
2000: \$50.2 million  
2008: \$65.3 million (decision made to reduce pharma influence)  
2010: \$55 million  
2012: \$42.6 million




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### Psychiatry Under the Influence

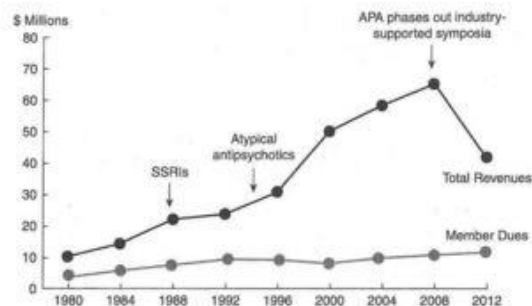


Figure 3.1 APA's annual revenues, 1980–2012.

Source: APA's annual financial reports, 1980–2012.

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## 1980: Moving Onward

- Bayh –Dole Act : law allowing researchers receiving federal grants to patent and profit from their discoveries.
- APA allows pharma to sponsor symposiums
- Financial conflicts with “KOLs”, Journal Editors, Textbook Writers, Clinical Guideline Authors, Diagnostic Criteria Developers, Psych Dept Chairs




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## Financial Conflicts of Interest among DSM IV and DSM 5 members

	DSM IV %	DSM 5 %
Task Force		
Work Panels	57	69
Anxiety	81	57
Eating Disorders	83	50
Mood Disorders	100	67
Sleep Disorders	50	100
Schizophrenia/Psychotic Disorders	100	83

Source: Cosgrove, PLoS Med (2012); used with permission

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- Field Trials testing DSM III
  - Determine *reliability*
  - Affirmed psychiatry’s “medical identity and commitment to scientific medicine” – G. Klerman
- DSM III intro: “It should be understood that for most of the categories the diagnostic criteria are based on clinical judgment, and have not yet been fully validated by data about such important correlates as clinical course, outcome, family history, and treatment response”
- Becomes the “Bible” of psychiatry

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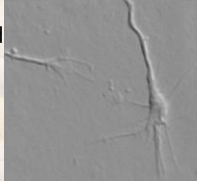
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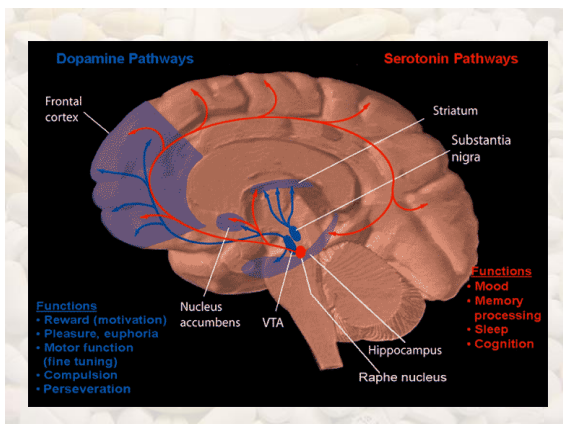
## Neurochemistry

- Dopamine
- Serotonin
- Norepinephrine
- *gamma* Aminobutyric acid
- Glutamate

[illegible]

## ***Monoamine Hypothesis***

- What is a *monoamine*?
  - Indolamine = Serotonin (5-HT)
  - Catecholamine = Dopamine (DA)  
Norepinephrine (NE)
- Where in brain?
  - Serotonin = *pons raphe nuclei*
  - Dopamine = *Ventral Tegmental Area (VTA)*
  - Norepinephrine = *pons locus coeruleus*

[illegible]

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*Low Serotonin Hypothesis of Depression*  
*High Dopamine Hypothesis of Schizophrenia*

- **Reserpine** "Induced depression in hypertension"
- **Iproniazid** "Psychic energizer in TB treatment"
- **Imipramine** "The first antidepressant"
- **Chlorpromazine and Amphetamine** "Effects on dopamine"

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The beginning of a theory.....  
 (circa 1960)

"Chemical imbalances in the brain"

- Chlorpromazine blocked dopamine (perhaps too much dopamine caused psychosis)
- Amphetamines increased dopamine activity, and triggered psychosis (lent to hypothesis)
- TCAs and MAOIs increased serotonin and norepinephrine in synapse (perhaps depression was due to low levels)

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1984: *The Broken Brain*, by Nancy Andreasen:  
 "Major psychiatric illnesses are diseases"

1984: "The Mind Fixers", by Jon Franklin (Baltimore Evening Sun). Pulitzer Prize

1985: NIMH Scientist Candace Pert: "People who act crazy are acting that way because they have too much or too little of some chemicals that are in their brains....Its just physical illness!"

"By 2006, 87% of Americans surveyed *"knew"* that mental health disorders were caused by a chemical imbalance"

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1988: Prozac to market

-5 months later, NIMH launched "Depression Awareness, Recognition and Treatment (DART) campaign.

"Depressive disorders are common, serious and treatable"

"Treatment is able to *restore* chemical imbalances"

(Eli Lilly paid for printing and distribution of 8 million DART brochures)




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## Some science....

- Dopamine is metabolized to homovanillic acid (HVA)
- Serotonin is metabolized to 5-hydroxyindole acetic acid (5-HIAA)  
- "Differences in cerebrospinal fluid not found" 1971, 1974, 1984
- APAs *Textbook of Psychiatry* (1999) states that there is no confirmation from the field that the monoamine hypotheses of depression and/or psychosis is true.
- Other publications state that PET studies, monoamine depletion studies, genetic polymorphisms fail to find evidence of monoamine neurotransmission in the pathophysiology in depression

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## Additional science.....

- Schizophrenia hypothesized to be due to excess dopamine utilization
- *Antipsychotic drugs cause cells to increase density of D2 receptors.*  
(complex neurology involving the prefrontal cortex, pyramidal cells, thalamus, mesolimbic and mesocortical pathways of neurons)

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- Drug treatments did not produce disease specific responses, but rather produced similar responses in people with different diagnoses.....***"Therefore, do DSM diagnoses identify real diseases, or merely convenient ways of grouping psychiatric symptoms?"***

—DSM -5 Task Force

- DSM = reliability, not validity

## Drug Testing

- Double blind, randomized controlled studies are standard for drug trials
- "Data mining" or an analysis with the purpose of identifying a result that favors the study drug
- Raw data to scientific paper to public pronouncement.(Chain of info that offers access)
- *What drug companies say vs.  
What academic psychiatrists (consultants) say*

## Alprazolam (Xanax, Upjohn), 1981 for anxiety. Tested for panic disorder, new DSMIII disorder

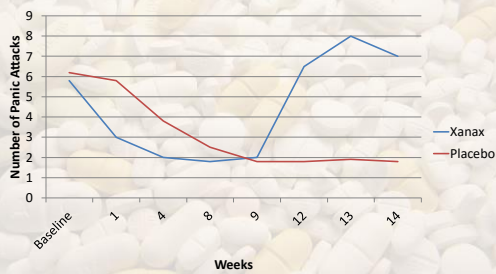
- "Cross National Collaborative Panic Study"
  - short term efficacy studies (4 weeks used as endpoint in data instead of 8 weeks)
  - adverse effects
  - discontinuation (data use excluded patients that had to withdraw from study due to needing to put back on drug, therefore smaller numbers became *statistically insignificant*)

### Data Published to Report Efficacy



Source: Arch Gen Psychiatry 45 (1988)

### Data



### "Panic Disorder"

- Educational efforts, APA symposia, "Dear Doctor" letters, conferences, workshops
- Anxiety and panic disorder: "Under-recognized and undertreated"

**FDA approved Xanax for panic disorder in 1990**

-1993, Xanax is 5<sup>th</sup> most frequently prescribed drug





## DSM and Anxiety

- Anxiety neurosis (DSM II) - - - Panic Disorder and GAD (DSMIII)
- Poor Impulse Control became (1) pathological gambling (2) kleptomania (3) pyromania (4) isolated explosive disorder
- Disclaimer in DSM IV: "no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder"

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## Fluoxetine (Prozac) clinical trials

- Hamilton rating Scale for Depression: Showed fluoxetine to be overall ineffective, only 1 point better than placebo, clinically insignificant
- Clinical trial data reported from investigators ultimately differed from FDA data, and falsely reported benefits of Prozac

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The HAM-D is designed to rate the severity of depression in patients. Although it contains 21 items, calculate the patient's score on the first 17 answers.

<p><input type="checkbox"/> 1. <b>DEPRESSED MOOD</b> (Gloomy attitude, pessimism about the future, feeling of sadness, tendency to weep) 0 = Absent 1 = Sadness, etc. 2 = Occasional weeping 3 = Frequent weeping 4 = Extreme symptoms</p> <p><input type="checkbox"/> 2. <b>FEELINGS OF GUILT</b> 0 = Absent 1 = Self-reproach, feels he/she has let people down 2 = Ideas of guilt 3 = Present illness is a punishment, delusions of guilt 4 = Hallucinations of guilt</p> <p><input type="checkbox"/> 3. <b>SUICIDE</b> 0 = Absent 1 = Feels life is not worth living 2 = Wishes he/she were dead 3 = Suicidal ideas or gestures 4 = Attempts at suicide</p> <p><input type="checkbox"/> 4. <b>INSOMNIA - Initial</b> (Difficulty in falling asleep) 0 = Absent 1 = Occasional 2 = Frequent</p> <p><input type="checkbox"/> 5. <b>INSOMNIA - Middle</b> (Complaints of being restless and disturbed during the night. Waking during the night.) 0 = Absent 1 = Occasional 2 = Frequent</p>	<p><input type="checkbox"/> 6. <b>INSOMNIA - Delayed</b> (Waking in early hours of the morning and unable to fall asleep again) 0 = Absent 1 = Occasional 2 = Frequent</p> <p><input type="checkbox"/> 7. <b>WORK AND INTERESTS</b> 0 = No difficulty 1 = Feeling of incapacity, listlessness, indecision and vacillation 2 = Loss of interest in hobbies, decreased social activities 3 = Productivity decreased 4 = Unable to work. Stopped working because of present illness only. (Absence from work after treatment or recovery may rate a lower score).</p> <p><input type="checkbox"/> 8. <b>RETARDATION</b> (Slowness of thought, speech, and activity; apathy; stupor) 0 = Absent 1 = Slight retardation at interview 2 = Obvious retardation at interview 3 = Interview difficult 4 = Complete stupor</p> <p><input type="checkbox"/> 9. <b>AGITATION</b> (Restlessness associated with anxiety.) 0 = Absent 1 = Occasional 2 = Frequent</p> <p><input type="checkbox"/> 10. <b>ANXIETY - PSYCHIC</b> 0 = No difficulty 1 = Tension and irritability 2 = Worrying about minor matters 3 = Apprehensive attitude 4 = Fear</p>
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## "Depression"



- 1986 survey of depression revealed that only 12% of Americans sought treatment for depression.
- Enter the **DART program, (Depression Awareness Recognition and Treatment)** launched by NIMH in 1988 (New NIMH Director who came from APA Public Affairs Dept)
  - "Unrecognized, undertreated"
- -"Recovery rates with medications have been shown to be in the range of 70 – 80% in comparison with 20 – 40% for placebo"
- -NIMH published info previously to the contrary

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## "Headlines"

- Newsweek: *Wonder Drug for Depression*
- NY Times: *"one of the best antidepressants ever designed"*
- Sixty Minutes: *"doctors now believe that chronic depression was caused by a chemical imbalance in the brain"*
- Time: *"Today, depression can be treated, quickly and effectively, in 7 cases out of 10"*

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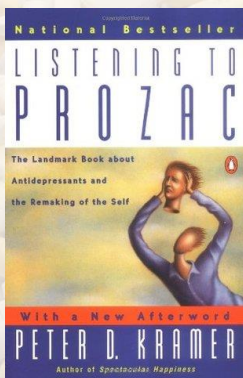
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## *“Dirty Little Secret”*

- Zoloft studies lack evidence of efficacy, yet still approved by FDA. Data manipulated. Celexa, Paxil follow.

“Dirty Little Secret” exposed in 2008 by Irving Kirsch and Erick Turner, reviewing FDA data for 12 anti depressants.

- trials of **Prozac, Effexor, Serzone and Paxil** dropped HAM-D scores 9.6 points, where placebo dropped scores 7.8 points ( *a difference of only 1.8 points. 3 points generally accepted as statistically significant.* )

- It was determined that patients with baseline HAM-D over 25 (severely depressed) benefitted by more than 3 points

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## **AD Clinical Trial Efficacy**

- -double blind, randomized clinical trials considered best evidence by APA
- -meta-analysis done from 2000 onward of RCTs
- “a large body of literature supports the superiority of SSRIs compared to placebo in the treatment of major depressive disorder”
- -duration of study?
- -study design?
- -endpoints used to assess efficacy?
- Fact: Approx 75% of clinical trial results published in major journals are industry funded, results in 5.3 times likelihood that study will find a positive result for the drug
- -negative studies are unpublished




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## **SSRIs**

Side effects: *sexual dysfunction, suppression of REM sleep, muscle tics, fatigue, emotional blunting, apathy, memory impairment, problem-solving difficulties, loss of creativity, learning deficiencies*

(Concerns with *hippocampus death, shrinkage of thalamus, frontal lobe abnormalities, Subcallosal cingulate activity*)

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## DSM Strategy

- > Expand potential pool of patients through APA diagnostics (create new diagnoses/loosen criteria)
- > Hire academic psychiatrists to conduct studies of the drugs for these new patient populations
- > Hire Marketing Firms to create papers, accumulate data: "Publication Planning"
- > Same psychiatrists become "Key Opinion Leaders", speak at conferences about validity of illness and drugs
- > "Grow the Market" through collaboration of APA, Marketing Firms, and Drug Industry




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## "Ghostwriting"

- Intramed
- Axis Healthcare Communications
- Excerpta Medica
- Current Medical Directions
- Edelman Medical Communications
- Complete Healthcare Communications

*"Third party technique of marketing"*

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## ADHD: Organic Brain Syndrome

- DSM I "Organic brain syndrome" (reaction of childhood)
- 1956 Ritalin (Ciba Geigy) for narcolepsy began to be used for hyperkinetic children
  - 150,000 children taking it by end of 1970's
- DSMIII Attention Deficit Disorder (inattention, impulsivity, hyperactivity)
  - disorder said to affect up to 3% of children
- DSMIIIR Attention Deficit Hyperactivity Disorder
  - 600,000 children diagnosed by end of 1980's
- DSMIV: 3 subtypes exist: inattentive only/hyperactive-impulsive only/both
  - disorder said to affect 3 – 5% of children

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## Enter Shire Pharma and Adderall (FDA approved for ADHD)

\*With Ritalin going off patent, industry dollars slowed down

- 1995: 6 – 9% of children had ADHD  
-(Joseph Biedermann, Harvard)
- 2012: 10% of youth ages 4 – 18 have been diagnosed  
-3.5 million youth prescribed an ADHD medication  
-6 x number in 1990

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## “How depressed are we?”

- 1966: prevalence rate of about 1.2%
- 1980's: NIMH's Epidemiologic Catchment Study (using DSM III) found 5% of adults depressed
- DSM III allowed a “dysphoric mood” along with 4 other symptoms from a list of 8, for two weeks to lead to a diagnosis.
- 1987: NIMH National Comorbidity Study reported 10% prevalence (using DSMIIIR criteria)

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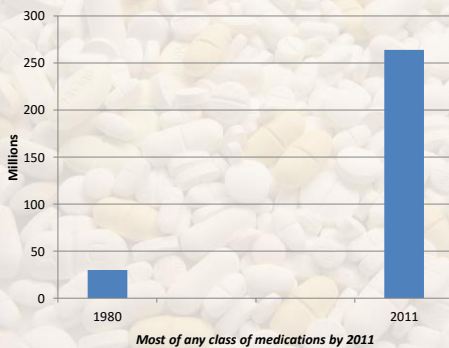
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## ANTIDEPRESSANT PRESCRIPTIONS




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## The Mood Disorders

- 1996: National Depressive and Manic – Depressive Association (funding from Bristol Myers Squibb) conference on depression: “Depression is one of the most frequent of all medical illnesses and is severely undertreated.”
- DSM includes diagnoses such as *Dysthymia*, *Adjustment Disorder with Depressed Mood*, *Mood Disorder Not Otherwise Specified*

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## The Mood Disorders

- DSMIII parsed “anxiety neurosis” (an analytic term) into separate, discrete, *distinct* disorders
  - -agoraphobia, panic disorder, PTSD, social phobia, OCD, GAD
- Panic disorder reported as common, but others rare
- Xanax approved by FDA in 1981 for panic disorder

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## The Mood Disorders

- National Comorbidity Studies of NIMH in early 1990s found greater prevalence of PTSD, social anxiety disorder and GAD.
- Zoloft (Pfizer) and Paxil (SKB) competing with Prozac (Lilly) in AD market.
  - Strategy developed to go after anxiety market
- Academics (KOLs) were recruited for development, advisory boards for clinical trials, oversight of trials, author of reports, speakers at conferences ("Selling the Disease")

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## Paxil

- 1993 SKB Advisory Board headed by James Ballenger
  - Ballenger was involved with Upjohn's trials for anxiety in 1980s
  - He served on DSMIIIR and DSM IV work panels for anxiety
  - Appointed head of *Paroxetine Panic Disorder Study Group* for SKB
  - led to announcement of prevalence of panic disorder and need for maintenance medication

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## Paxil "The Anxiolytic Antidepressant"

- Paxil approved for S.A.D. in 1999. It was beginning to be described as very common (8%), behind only depression and alcohol dependence as mental disorders in US
- Paxil approved for PTSD in 2001. "Lifetime prevalence of around 9%" - Jonathan Davidson, KOL for SKB
- Paxil approved for GAD in 2001, replaced BZDs as first line therapy

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## Paxil Marketing Strategy

- The Medicine Group: Ghostwriters in UK, hired to write "Paxil Publication Plan" and "Paroxetine-Efficacy across the Spectrum"
- Scientific Therapeutics Information (STI) hired in US
- PsychNet: Speakers bureau created by GlaxoSmithKline in 2000 to recruit and educate key influential psychiatrists and physicians. "Contemporary Issues in Anxiety Spectrum Disorders" was one workshop.
  - reviews the prevalence, treatment options, and efficacy of Paxil
- 2002: Paxil become best selling AD globally

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- 2015 Top selling ADs (IMS Health)
  1. Cymbalta
  2. Pristiq
  3. Viibryd
  4. Celexa
  5. Zoloft
  6. Prozac
  7. Desyrel
  8. Lexapro
  9. Paxil
  10. Effexor
- Abilify had \$9.3 billion in sales (2014)
  - patent expired in 2014 (Otsuka Pharma)
- Rexulti (brexpiprazole) (Otsuka Pharma)
  - introduced in 2014, FDA approved in 2015




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## CPG recommendations for initial treatment for mild depression

(source: J Eval Clin Prac)

Intervention	US Guidelines	UK Guidelines	Netherlands Guidelines
Antidepressant	YES	NO	NO
Psychotherapy	YES	YES	YES
Antidepressant plus psychotherapy	YES	NO	NO
Other somatic therapies	YES	NO	NO
Lifestyle	NO	YES	YES
Low intensity psychological	NO	YES	YES

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## By 2008, 11% of American adults were taking a daily Antidepressant

- Early reports of long term AD therapy led to more frequent relapsing. (1970s)
- 1990 NIMH study for 18 months compared imipramine to psychotherapy and placebo. (imipramine group fared worst)
- Kirsch, Fournier, Turner, Star\*D, Rush: All studies that found decreased effectiveness with ADs
- NIMH six year study, N=547, "untreated individuals had milder and shorter-lived illnesses"

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## "Spellbound"

- "Depressogenic" theory of AD use begins to circulate
- APA depression guidelines: Did not discuss issues of decreased response, but stated that ADs be used for "maintenance therapy"
- Rif El-Mallakh, Univ of Louisville School of Medicine: "Tardive Dysphoria"
  - manifests as a chronic dysphoric state that is initially transiently relieved by , but ultimately becomes unresponsive to ADs

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## ADHD Guidelines

- AACAP (American Academy of Child and Adolescent Psychiatry)
- NICE (National Institute for Health Care Excellence) UK
- Guidelines developed by AACAP committee in 2007, led by Steven Pliszka, prof of psychiatry at Univ of Texas, San Antonio
  - Pliszka: consultant and speaker for Shire Pharma (Adderall and Vyvanse)
- Guidelines: stimulants as first line treatment for children and adolescents of all ages
  - (also recommends off label use of other meds for nonresponders (ADs, antihypertensives))
- NICE guidelines recommend "group-based parent training and education programs" as first line for school age children (medication reserved for severe symptoms and impairment, or as 2<sup>nd</sup> line)

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## Multisite Multimodal Treatment Study of Children with ADHD (MTA Study)

- Compared medicated vs. nonmedicated groups of children
  - 14 months
  - 36 months
  - 6 years
- "Outcomes similar at 14 months, but significantly different at later periods"
- "Published data abstractly reported"

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- *NO genuine informed consent* **Informed Consent (or lack thereof)**
- Misinformation (chemical imbalance theory); lack of information (i.e. failure to disclose poor long term results)

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## SSRI: Withdrawal

- Persistent withdrawal effects *six weeks* after cessation of taking SSRI antidepressants.
- Researchers reviewed self-reporting adverse events between February 2010 and September 2010 and found post-withdrawal symptoms "**may last several months to years.**"
- Reported symptoms included disturbed mood, emotional lability, irritability, and poor stress tolerance

Source: *Psychotherapy and Psychosomatics Journal*, October 2012

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- Significant persistent postwithdrawal emergent symptoms noted consist of anxiety disorders, including generalized anxiety and panic attacks, tardive [developing slowly] insomnia, and depressive disorders including major depression and bipolar illness.
- Anxiety, disturbed mood, depression, mood swings, emotional lability, persistent insomnia, irritability, poor stress tolerance, impaired concentration and impaired memory
- Dr. John Zajecka reported in the *Journal of Clinical Psychiatry* that the agitation and irritability experienced by patients withdrawing from one SSRI antidepressant could cause "aggressiveness and suicidal impulsivity."

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## FDA

- Withdrawal studies not required
- Only concerned with drug's safety and efficacy while it is being taken.

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- **Antidepressants and Neuroleptics**
  - flu-like syndrome with headache, muscle aches, chills, nausea, vomiting, diarrhea, and loss of appetite
  - muscular reactions such as uncontrollable rhythmic movements and tremors (these are more severe with neuroleptics)
  - insomnia, emotional distress, feeling like one is "going crazy"
- **Lithium**
  - less side effects generally than other classes
  - insomnia, anxiety, irritability.
- **Minor Tranquilizers, Sedatives**
  - sudden withdrawal can result in life-threatening seizures; withdrawal must be very gradual
  - seizures common in early stages of withdrawal
  - other reactions can include flu-like syndrome (see above), muscle tics, restlessness, and anxiety
  - withdrawal symptoms usually take a few days to develop, but can occur immediately and get worse during the first week.

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## Medication Withdrawal Strategy

- Establish a collaborate, trusting and empathic team approach to psychiatric drug withdrawal
- Recognize common, serious and sometimes overlooked adverse drug effects that may require drug withdrawal
- Treat emergencies during drug therapy and during withdrawal
- Identify common withdrawal reactions for every type of psychiatric drug
- Determine the first drugs to withdraw during multi-drug therapy
- Distinguish between withdrawal reactions, newly occurring emotional problems, and the recurrence of pre-medication problems
- Estimate the length of withdrawal
- Prescribe very small doses of medication when necessary
- Understand how "medication spellbinding" (intoxication anosognosia) makes patients unaware of the adverse mental and emotional effects of their drugs during treatment and withdrawal

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## NIDA

- Effective medications exist for treating opioid, alcohol, and nicotine addiction and for alleviating the symptoms of many other mental disorders, *yet most have not been well studied in comorbid populations.*
- Some medications may benefit multiple problems. For example, evidence suggests that bupropion (trade names: Wellbutrin, Zyban), approved for treating depression and nicotine dependence, might also help reduce craving and use of the drug methamphetamine.
- *"Clearly, more research is needed to fully understand and assess the actions of combined or dually effective medications."*

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## Examples of Behavioral Therapies for Patients with Comorbid Conditions

- Multisystemic Therapy (MST)
- Brief Strategic Family Therapy (BSFT)
- Cognitive-Behavioral Therapy (CBT)
- Therapeutic Communities (TCs)
- Assertive Community Treatment (ACT)
- Dialectical Behavior Therapy (DBT)
- Exposure Therapy
- Integrated Group Therapy (IGT)

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## Medication Use

### • **Antipsychotics**

chlorpromazine	Thorazine	1952
clozapine	Clozaril	1990
risperidone	Risperdal	1993
olanzapine	Zyprexa	1996
aripiprazole	Abilify	2002

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## Antipsychotics

• Paliperidone	Invega -Trinza, Sustenna
• Olanzapine	Zyprexa -Zydis, Relprev
• Asenapine	Saphris
• Clozapine	Clozaril, Fazaclo, Versacloz
• Aripiprazole	Abilify -Maintena, Discmelt
• Quetiapine	Seroquel -XR
• Lurasidone	Latuda
• Risperidone	Risperdal -M-Tab, Consta
• Cariprazine	Vraylar
• Brexpiprazole	Rexulti
• Iloperidone	Fanapt
• Ziprasidone	Geodon
• Pimavanserin	Nuplazid

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## Medication Use

### • **Antidepressants**

imipramine	Tofranil	1958
fluoxetine	Prozac	1988
sertraline	Zoloft	1991
paroxetine	Paxil	1992

### • **Antimaniacs**

lithium	Eskalith	1949
valproic acid	Depakote	1967
lamotrigine	Lamictal	2003
topiramate	Topamax	1996 (off label)
gabapentin	Neurontin	1993 (off label)

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## Antidepressants

- MAOIs (1950's, *iproniazid*)
- TCAs (1950's, *imipramine*)
- SSRIs
  - Citalopram
  - Escitalopram
  - *Fluoxetine*
  - Fluvoxamine
  - Paroxetine
- SNRIs
  - Desvenlafaxine
  - Duloxetine
  - *Venlafaxine*
  - Milnacipran
  - Levomilnacipran
- Atypicals
  - Bupropion
  - Mirtazapine
  - Trazodone
  - Nefazodone
  - Vilazodone
  - Vortioxetine

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## Medication Use

- **Anti-Anxiety Agents**

Meprobamate	Miltown	1955
Benzodiazepines		
Chlordiazepoxide		1960
Diazepam		1963
(By 1983, 17 BZDs on market)		
- FDA Committee in 1979 determined hypnotic effects of BZDs work < 2 weeks; anxiolytic effects <4 months

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## Medication Use

- **Stimulants** (ADHD, ADD)
 

amphetamines	1932	(Benzedrine)
	1996	(Adderall)
lisdexamfetamine	2007	(Vyvanse)
methylphenidate	1954	(Ritalin, Concerta)
dexmethylphenidate	2006	(Focalin)
atomoxetine	2001	(Strattera)

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## Clinical Trials

- New drug indication allows 3 additional years of patent exclusivity
- Must examine the Financial Conflict of Interest (FCOI) of DSM panel members and trial principal investigators for manufacturers
- “No biological markers” available.....subjective discretion used to widen diagnostic boundaries.
- “Ghost Writers” – academics and Industry marketers

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## Pharma Research and Marketing

- Pharmaceutical Industry is the largest funder of clinical trials in the US (60%)
- \$30 Billion a year spent on drug development
- “Publication Bias”
- “Skewed results”
- Statistical significance?
- Misinterpretation
- Off label use promotion

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## Current Drug Trials Summary

Trail Drug	Trial Indication
Duloxetine (Cymbalta)	Bereavement-related depression
Citalopram (Celexa)	Complicated grief
Armodafinil (Nuvigil)	Binge eating disorder
Duloxetine (Cymbalta)	Binge eating disorder
Lamotrigine (Lamictal)	Binge eating disorder
Lisdexamfetamine (Vyvanse)	Binge eating disorder
Arbaclofen	Autism Spectrum disorder
Methylphenidate (Daytrana)	Autism Spectrum disorder
Lisdexamfetamine (Vyvanse)	Severe mood dysregulation
Risperidone (Risperdal)	Severe mood dysregulation
Paroxetine (Paxil)	Premenstrual dysphoric disorder
Donepezil (Aricept)	Mild cognitive impairment

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## Marketing

After six decades of outlawing, of direct-to-consumer advertising of prescription drugs, the modern marketing of Ambien and Adderall, Paxil and Prozac, or Zyban and Zyprexa illustrates that prescribed medications are no longer exclusive tools of medical practice: Medications can now be sought or declined on the basis of **consumer preferences**.

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## Atypical Antipsychotics

1. Risperdal (Janssen)
2. Zyprexa (Lilly)
3. Seroquel (AstraZeneca)

### *Eli Lilly settles Zyprexa lawsuit for \$1.42 billion*

-Drug maker pleads guilty to illegally marketing drug for unapproved use



**Pharmaceutical Giant AstraZeneca to Pay \$520 Million for Off-label Drug Marketing**




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## Risperdal

2010: State of Texas sued Johnson & Johnson for illegal marketing of Risperdal

-this allowed David Rothman, professor of social medicine at Columbia Univ Medical School to serve as an expert witness, and thus review internal J&J documents

-Janssen (Division of J&J), engaged 3 experts to produce a consensus guideline for Risperdal as treatment for schizophrenia. 3 academic psychiatrists, received a \$450,000 unrestricted grant from Janssen. Produced the "Tri-University Guidelines" after 7 months. This was published in the Journal of Clinical Psychiatry.

"Recommended Risperdal and other 2<sup>nd</sup> Gen drugs as first line treatment.

-They also formed Expert Knowledge Systems (EKS) to help market drug, and adopt the guidelines.

-Done through CME programs. 3 experts earned \$427,659

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## Pharma and the US Dept of Justice

- Lawsuits
  - Abilify = compulsive behaviors
  - Cymbalta = withdrawal
  - Paxil, Prozac = increased suicidality
  - Risperdal = metabolic disorders
  - Zyprexa = diabetes

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## Psychotropic Drug Lawsuits

- |        |               |                      |        |
|--------|---------------|----------------------|--------|
| • 2001 | Zoloft, Paxil | "Homicidal Behavior" |        |
| • 2002 | Prozac        | "Suicide Attempt"    | \$6.5M |
| • 2003 | Paxil         | "US Medicaid Fraud"  | \$87M  |
|        | Zoloft        | "Suicidality"        |        |
| • 2004 | Zyprexa       | "Diabetes"           |        |
|        | Zoloft        | "Suicide"            |        |
|        | Paxil         | "Suicidality"        | \$2.5M |
|        | Remeron       | "Antitrust"          | \$60M  |

Source: Citizens Commission on Human Rights  
[www.cchr.org](http://www.cchr.org)

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## .....continued

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|--------|---------|---------------------|--------|
| • 2005 | Zyprexa | "Diabetes"          | \$690M |
|        | Zoloft  | "Suicide"           |        |
| • 2006 | Abilify | "Illegal marketing" | \$500M |
| • 2007 | Paxil   | "Children Dangers"  | \$64M  |
| • 2008 | Zyprexa | "Illegal marketing" | \$15M  |
|        | Abilify | "Illegal marketing" | \$4M   |
|        | Paxil   | "Suppressed data"   | \$40M  |
|        | Zyprexa | "Illegal marketing" | \$62M  |

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### .....continued

- 2009 Zyprexa "Unlawful promotion" \$1.3B
- Risperdal "False advertising" \$4M
- Zyprexa "Unlawful promotion" \$15M
- Zyprexa "Unlawful promotion" \$23M
- Geodon "Unlawful promotion" \$2.3B
- Paxil "Birth defects" (800 cases)
- 2010 Seroquel "Diabetes" \$198M

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### Additional/Current Issues

- Abilify - Compulsive behaviors, gambling. Lawsuits pending
- Cymbalta – Severe withdrawal symptoms. Lawsuits pending
- Lexapro/Celexa – Unapproved marketing, failure to disclose negative clinical trial results, kickbacks to docs. \$313M settlement
- Paxil – Increased risk of suicide in children
- Prozac – Suicidality, birth defects

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### Additional/Current Issues

- Risperdal, Invega– Marketing for use in children, which was not FDA approved. Also concealed side effects of diabetes, substantial weight gain and gynecomastia. Multiple state lawsuits.
- Abbot and Omnicare kickback scheme with Depakote in nursing homes. \$1.5 B settlement

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## Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents

Table 2. Draft Advertising and Promotion Budget for Gabapentin for 1998, by Strategy and Tactical Category\*

Tactical Categories, with Examples†	Budget, in Thousands of Dollars‡				Total Budget in Thousands of Dollars
	Expand Neurontin Use in Epilepsy Monotherapy	Conduct Targeted Promotional/CME Efforts on High-Prescribing Physicians	Develop and Leverage Thought Leader Support	Maximize Opportunities in "Emerging (Unapproved) Uses"	
CBU/SPE	5300	1500	1600	0	8400
Professional education (e.g., speakers bureau, advisory boards, dinner meetings)	6229	0	1842	11 039	19 110
National speaker (e.g., physician honoraria and travel, speaker programs)	2110	900	950	0	3160
Direct mail	900	0	0	0	900
Professional promotional literature (e.g., conversation giveaways, patient brochures)	2240	100	620	0	2960
Medical journal (e.g., journal advertising)	1200	0	0	0	1200
Grain merchandise (e.g., patient assistance programs)	700	100	50	0	850
Samples	800	300	100	0	1200
Displays, agency fees, pack/ship, miscellaneous (e.g., convention displays)	1570	150	0	0	1720
Market research	400	0	0	100	500
Total	21 449	2650	4762	11 139	40 000

\* The meaning of the term "CBU/SPE" is unclear, although "CBU" typically refers to "customer business units," regional divisions of Parke-Davis. CME = continuing medical education.

† Tactical categories are listed as they appear in the source documents (12). Examples were taken from line items in budget planning documents assigned to each category, although no specific examples were available for certain categories.

‡ Sources were listed in budget planning documents as follows (12, 13): 1) "Expand Neurontin use in epilepsy through the introduction of monotherapy"; Parke-Davis had expected U.S. Food and Drug Administration approval for gabapentin as monotherapy for epilepsy, but the application was rejected. 2) "Conduct targeted promotional Call efforts on high-dose Neurontin & PCH (paraguard) care physicians to increase their overall Neurontin usage"; 3) "Continue to develop and leverage thought leader support throughout the community to maintain our leadership position and achieve our business potential"; 4) "To maximize opportunities in the 'emerging (unapproved) uses' through clinical trials, publications, and educational events."

## Numbers

- 1987 (year of Prozac) = 1.25 million adults (18-65) on SSI/SSDI due to mental illness
- 2012 = 4.2 million adults (2.1 million for mood disorder; approx 1 million for schizophrenia)
- Psych drugs spending: 1987 = \$800 million
- 2012 = \$30 billion
- National Comorbidity Study of 2005: Anxiety/Mood Disorders/SUD = 29.4% in 1992
- 30.5% in 2003
- -Those receiving treatment jumped from 20.3% to 32.9% from 1992 to 2003
- -Those receiving disability benefits due to mental illness jumped from 1.5 million (1990) to 3.25 million (2003)

## Outcomes Schizophrenia

- 1940's – 1950's: 75% of first episode patients recovered in 3 years; 20% required continued hospitalization
- 1955: 267,000 schizophrenic patients (1 in 617)
- 1965: Medicare/Medicaid and "deinstitutionalization"
- 2010: 2.4 million schizophrenic patients (1 in 125)

## Outcomes Schizophrenia

- Clinical trials for 6 weeks
- “Brief Psychiatric Rating Scale”
  - 20% reduction in score is clinically significant
  - Symptoms: Anxiety, grandiosity, hostility, suspiciousness, unusual thought content, uncooperativeness, hallucinations
- 1961 trial of Thorazine: 75% of treatment group improved, 23% placebo group improved

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## Outcomes Schizophrenia

Chouinard and Jones “Supersensitivity Hypothesis”  
 Vermont Longitudinal Study  
 W.H.O. Cross Cultural Studies  
 Tardive Dyskinesia/Cognitive Decline Studies  
 MRI Studies  
 Nancy Andreasen Longitudinal MRI Study  
 NIMH Follow Up Study

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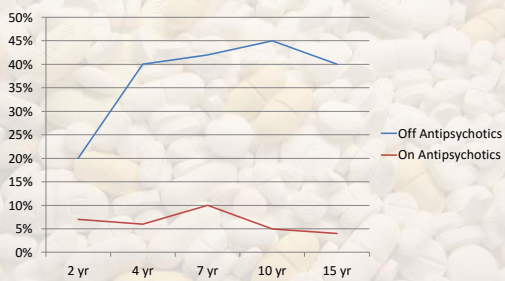
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## Harrow, M *Journal of Nervous and Mental Disease*, 2007




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## **“Antipsychotics”**

- Decrease Dopamine release by antagonizing (blocking) D2 receptor activity
- Reduce positive (+) symptoms of hallucinations and delusions.
- Not effective with negative (-) symptoms of apathy, cognitive impairment, reduction in speech, blunted emotions, social withdrawal, impaired attention, anhedonia, lethargy
- Pronounced side effects: EPS, Dystonia, Akathisia, Tardive Dyskinesia

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## ***“The opposite of depression is not happiness, but vitality”***

- “Melancholia”
- Hippocrates prescribed Mandrake root
- “Mainly considered self-limiting”
- 1930’s – 1940’s: 1 in 1,000 patients
- 1955: 7,250 first admissions with a disability rate of 1 per 4,000
- 2010: Leading cause of disability in US for ages 15 – 44, affecting 15 million

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## ***Outcomes      Depression***

- “Placebo Response” recognized
- NIMH review in 1970: Medications minimally effective
- 1980’s NIMH studies: Only severely depressed responded to treatment vs placebo
- 1990s data reveals high incidence of relapse upon drug withdrawal
- “Chronification” of disease.
  - 1 in 10 affected
  - Earlier in life
  - Lifelong ailment

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## Outcomes      Depression

- *Center for Addiction and Mental Health of Ontario, 2003 Study:*
- Identified 1,281 people placed on short term disability between 1996 and 1998 due to depression
  - 9% of unmedicated went on long term disability
  - 19% of medicated

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## Outcomes      Depression

- UK Analysis of sick days due to depression and neurotic disorders:
  - 1984: 38 million
  - 1995: 117 million
- US working age disabled due to depression tripled during the 1990s
- 2006 study of *unmedicated* patients after initial episode of depression:
  - 23% at 1 month
  - 67% at 6 months
  - 85% at 1 year

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## Outcomes      Anxiety

- Long term use leads to increased anxiety, panic attacks and agoraphobia, decreased social skills, deterioration of personal care, poor coping skills, as well as cognitive impairment and functional decline
- 2007 study showed 75% report increased symptoms
- Maine Benzo Study Group in 2002
- “Affective Disorders” increase six-fold on SSDI

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## BiPolar

- SSRI Trial review: 8% treated youth experienced manic/hypomanic episode (0.2% placebo)
- Luci Bini Mood Disorders Clinic in NYC, 1998-2000: 84% of bipolar children had been prescribed medications; <10% unmedicated
- Time magazine report, 2002: "most children with bipolar illness are diagnosed with a different illness initially, mainly ADHD"
- 1996-2007 the number of total days of children hospitalized for psych diagnosis rose from 1.96 million to 3.64 million (Internal Medicine News)
- 2002: Psychology Today reported an increasing number of college students taking an antidepressant were experiencing "first episodes of mania"
- 2007: Number of children discharged from hospitals with a bipolar diagnosis rose fivefold from 1996 to 2004 (Biol Psych)
- 1987 = 16,200 children on SSI due to mental disorder (5% of total recipients)
- 2011 = 728,000 (58% of total)

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## Outcomes Bipolar Disorder

- 1955: 1 in 13,000 diagnosed
- Today affects 1 in 40
  - 1/3 – 2/3 present as substance abusers
  - Antidepressant use (Studies show 3x rate with antidepressant use)
- 1996 – 2004: Diagnoses increased by 56%

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## Outcomes Bipolar

- Prior to 1960: 1/3 of patients had > 3 manic episodes in a *lifetime*
- 1960 – 1970: 2/3 of patients became chronic
- 1980s: 16% "rapid cyclers" with > 6.5 manic episodes a *year*
- 2008 NIMH study (STEP-BD):
  - Antidepressant use = 4x likely to rapid cycle
  - 2X likely to have multiple manic/depressive episodes

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## Outcomes *Bipolar*

- NIMH study 1978-1981:
  - Bipolar I patients were depressed, manic hypomanic or having mixed symptoms a significant amount of the time.
- 2004 study at New Jersey Medical School:
  - 33% of Bipolar I and 22% of Bipolar II patients were rapid cyclers. Both groups symptomatic nearly half the time.

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## Bipolar in the Modern Era

	Pre Lithium	Medicated
Prevalence	1 in 5,000 to 20,000	1 in 20 to 50
Good long term functional outcomes	75% to 90%	33%
Symptom course	Time limited acute episodes of mania and major depression with recovery to euthymia and favorable functional adaptation between episodes	Slow or incomplete recovery from acute episodes, continued risk of recurrences and sustained morbidity over time
Cognitive function	No impairment between episodes of long term	Impairment in many cognitive domains, similar to what is observed in schizophrenia

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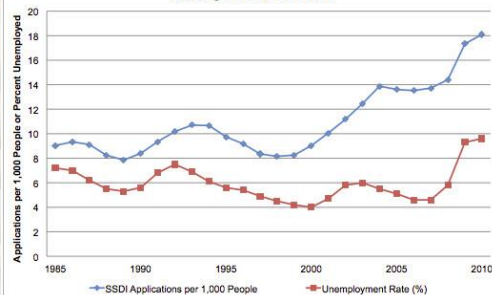
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Figure 5: SSDI Applications per 1,000 Adults and U.S. Unemployment Rate, Ages 25-64, 1985-2010




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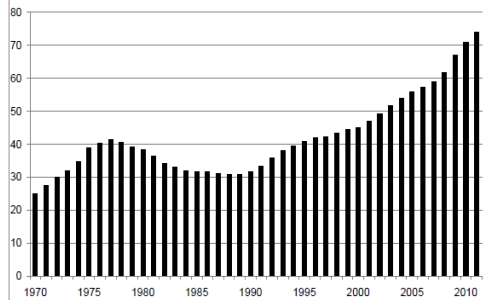
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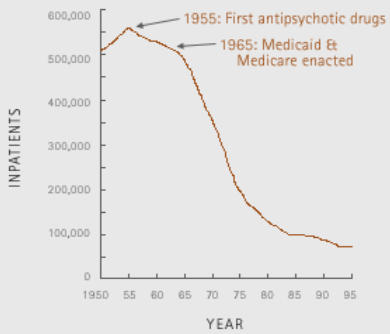
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Figure 3. Disability Recipients per Thousand U.S. Workers

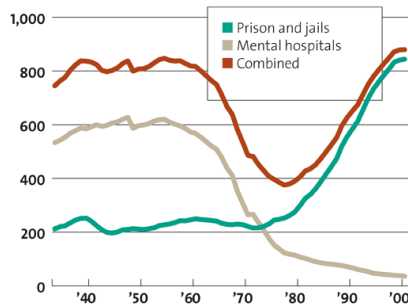


Source: Social Security Administration and Bureau of Labor Statistics.



### Locked Up. But Where?

Rates of institutionalization, per 100,000 adults





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- Cosgrove, et al, *"Conflicts of interest in DSM 5"*

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- Melody Petersen; *"Our Daily Meds"*
- Dirty Little Secret; Irving Kirsch and Erick Turner

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