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Psychopharmacology: Advances & Challenges

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Disclosures–2007

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Is a consultant to, or has collaborated in research with: Alkermes, Auritec, Biotrofix, IFI, Janssen, JDS, Lilly, Merck, NeuroHealing, Novartis, and Solvay Corporations

US annual illness costs

Diagnosis	$B/yr
Mental illness + dementia	260
All cardiovascular disease	160
CNS injuries	106
Cancer	104
Major affective disorders	90
AIDS	66
Coronary artery disease	43
Arthritis	38
Schizophrenia	33
Strokes	18

From Greenberg et al: J Clin Psychiatry 1993; 54: 419–424. Includes indirect costs from lost income and early death (e.g., MADs: 28% direct treatment-costs + 55% lost income & productivity in illness + 17% due to suicide).

US Pharmaceutical Market

Drug Class	Share (%)	$B/Yr
Cardiovascular	27	11
Psychotropic	26	11
Gastroenterological	18	8
Antibiotic	18	8
Anticholesterol	11	6

Total for No. Amer. = $116B/yr (38% of $300B world market), with ca. 7%/year growth. Leading psychotropics are SRIs ($6B), atypical antipsychotics ($3B), anticonvulsant-mood stablizers ($2B). Data from *Drug Topics* 2000.

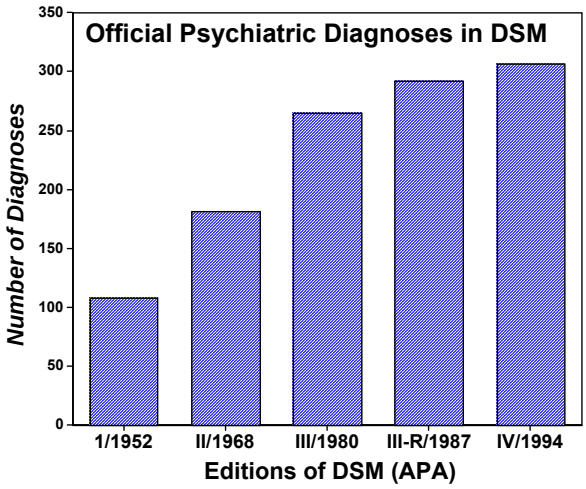
Beginnings of modern psychopharmacology: 1950–1960

- **Lithium carbonate (1949)**
- **Reserpine (1952)**
- **Chlorpromazine (1952)**
- **Ipronizaid (1954)**
- **Imipramine (1957)**
- **Haloperidol (1960)**
- **Chlordiazepoxide (1960)**
- **Clozapine (1960)**

Note: **All of these breakthrough discoveries were largely** *serendipitous*.

An industrial-academic-regulatory complex emerges: 1970s–80s

- **Biochemical & receptor screening replace bioassays**
- **Consolidation of pharmacocentric biological psychiatry**
  (leaping from partial pharmacodynamics to "pathophysiology")
- **Standardization of "efficacy" trials for regulatory review**
  (oversimplified p-worship; placebo vs. "not different = equal" fallacy; rarity of adequate long-term trials of prophylactic effectiveness)
- **Do syndromes produce treatments, or vice-versa?**
  (e.g., "antihyperactivity, antipsychotic, antidepressant, anxiolytic, antimanic, antipanic, antiobsessional agents")
- **Treatment-encouraged proliferation of "official" diagnoses**
  van Praag: "What do you mean, 300 DSM diagnoses?!"
- **"Novel" (not necessarily better) agents emerge**
  (e.g., SRIs, atypical antipsychotics, anticonvulsants)



Pharmacocentric Cycle of Biopsychiatry

Examples:

Treatment	Diagnosis	Pharmaco-dynamics	"Patho-physiology"
Haloperidol	Schizoph renia	Anti-DA	DA-excess
Lithium	Bipolar disorder	Anti-CA	CA-excess
Imipramine	Major depression	Pro-NE	NE-deficiency
Alprazolam	Panic disorder	Pro-GABA	GABA-deficiency?
Fluoxetine	OCD	Pro-5-HT	5-HT-deficiency?

Status of Antipsychotic Drugs (APDs)

- All marketed APDs are effective, nonspecific, palliatives in mania & acute functional or organic psychoses
- Except for clozapine, modern APDs are nonsuperior in efficacy but have lower (non-zero) EPS risks than older APDs
- Long-term effectiveness is substantial vs. major episodic recurrences, but not core features or outcome in schizophrenia
- Newer APDs have few RCTs of ≥12 mos, often confounded by "enrichment" and "discontinuation" designs
- Modern APDs are far more expensive, with questionable cost/benefit relationships
- Risks with modern agents include metabolic syndrome, akathisia, rare atypical NMS & cardiac toxicity

Phase-2 CATIE trials

Measures	*Clozapine*	*Olanzapine*	*Risperidone*
Subjects (N)	43	83	83
Dose (mg/day)	332	21.1	4.2
Initial PANSS	90.3	80.3	75.4
PANSS Change (%)	–13.0	–9.3	–5.9
Discontinued (%)			
Any reason	58.1	67.5	67.5
Inefficacy	11.1	25.4	30.3
Intolerability	44.4	22.0	16.5
Mos to 50%-DC	10.5	5.6	6.3

From McEvoy et al. Am J Psychiatry 2006; 163: 600–610; Stroup et al. *ibid.*: 611–622.
Note: Perphenazine was indistinguishable from olanzapine or risperidone; clozapine (patented in 1960!) was only marginally superior to other agents, all of which produced minor symptom-changes with short retention times.

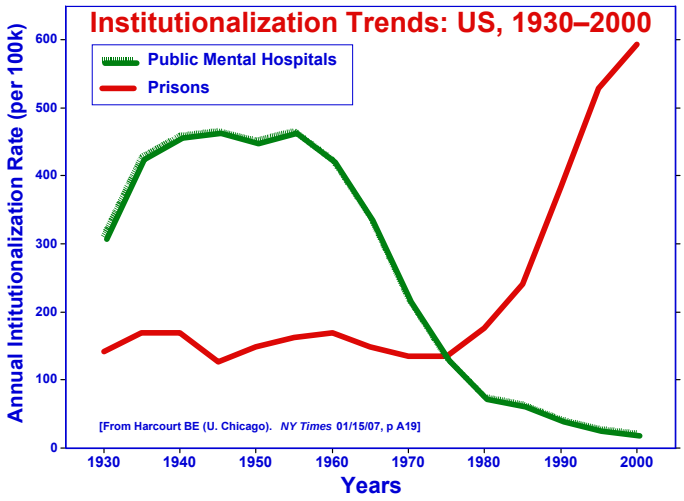
Antipsychotics: Adverse-effects Score-card

- **Dystonias & bradykinesia:** *much improved*
- **Akathisia:** *it still occurs*
- **Malignant syndrome:** *rarer, harder to recognize*
- **Tardive dyskinesia:** *much improved*
- **Clozapine:** *wonderful, but toxic*
- **Weight-gain & metabolic effects:** *major public health problems in the making?*

Long-term clinical outcome: Schizophrenia, 1895–1994

Years	%-Favorable Outcome
1895–1955	35.4%
1956–1985	48.5%
1986–1994	36.4%

From Hegarty JD, Baldessarini RJ, et al. Am J Psychiatry 1994; 151: 1409–1416.



Status of Antidepressant Drugs (ADDs)

- All marketed ADDs are effective in adult major depression MDD (>BP depression); most are also anxiolytic
- Only fluoxetine is approved for juvenile MDD; ADD efficacy in childhood MDD is unproved
- Modern ADDs are nonsuperior in efficacy to older ADDs but far less toxic on overdose
- ADD effects on suicidal risk remain unclear
- Long-term effectiveness is substantial in preventing relapses (6–12 mos); evidence of long-term prophylaxis is weak in MDD, poor in BP-depression, & unproved in anxiety
- Risks with modern ADDs include destabilization of BPD, PK-interactions, anorgasmia, GI sx, withdrawal sx

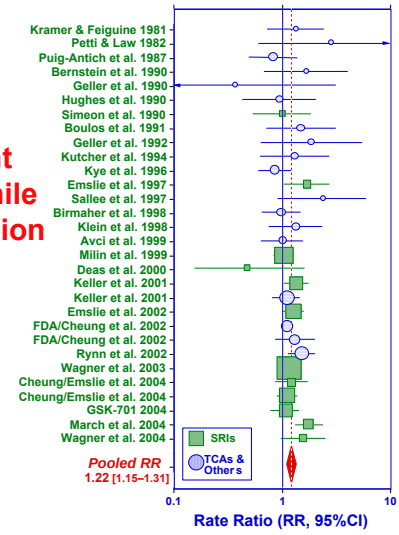
Antidepressant Efficacy: Responders to antidepressants vs. placebo

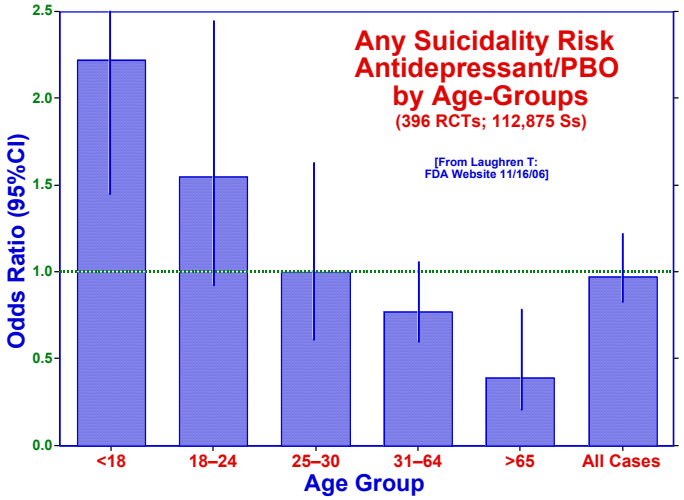
		Response Rates (%)		
Drugs	**N**	**Drug**	**Placebo**	***Difference***
TCAs	3,327	65.0	38.0	27.0
MAOIs	1,944	64.0	27.0	37.0
SSRIs	2,463	62.8	35.8	27.0
Atypical	277	48.0	20.0	28.0
Totals	8,011	62.2	33.1	29.1
NNT				3.4

From Fawcett & Barkin: J Clin Psychiatry 1997; 58 (Suppl 6): 32–39.
Note: NNT in adolescents: 8.3; children: 101 (Tsapakis et al. 2007).

Antidepressant Trials in Juvenile Major Depression

[Tsapakis et al. 2007]





Unintended consequences?

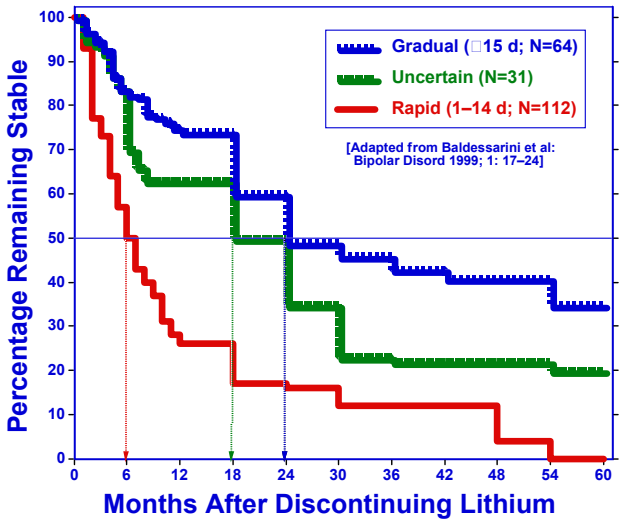
- SSRI sales: Declining since 2003 & not replaced by alternative treatments
- *New* MDD diagnoses by PCPs: Declining in adults & children
- Suicide rates: No longer declining after decreases paralleling massively increased market-penetration of SSRIs in 1990s

Based on: Valuck (U. Colorado) *Am J Psychiatry* 2007; in press;
Baldessarini et al. *Harvard Rev Psychiatry* 2007; in press.

Status of Mood-Stabilizing Drugs (MSDs)

- Li remains the best-established, most versatile MSD, & the only MSD with antisuicidal effectiveness
- All APDs are antimanic, as are CBZ & DVP
- LTG has solid long-term evidence vs. BP-depression (a major unsolved challenge)
- Most long-term MSD trials are confounded by "enrichment" (initial acute efficacy & tolerability of product-of-interest) & "discontinuation" (early Rx-removal) designs & short-duration
- DVP (prophylactic effectiveness unproved & unapproved) & LTG (not antimanic) dominate US market: *Do ease-of-use & marketing trump evidence?*
- Risks of MSDs: wt-gain, variable teratogenicity (DVP > CBZ >> Li), masculinization (DVP), hypokalemia (oxCBZ), rashes (LTG), acute & renal-thyroid toxicity (Li)

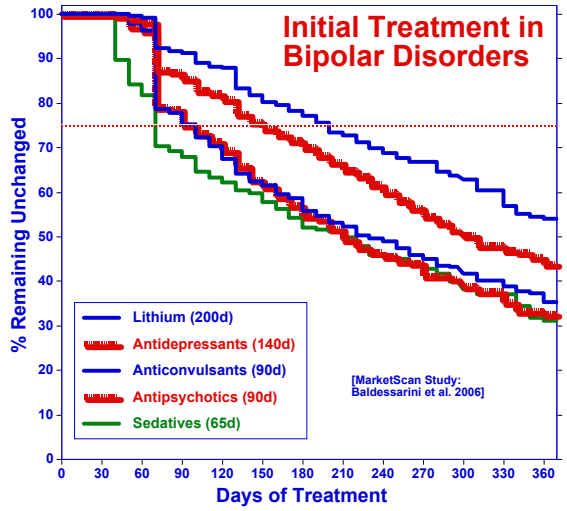
CBZ = carbamazepine, *DVP* = divalproex, *Li* = lithium, *LTG* = lamotrigine, *oxCBZ* = oxcarbazepine; *Rx* = treatments

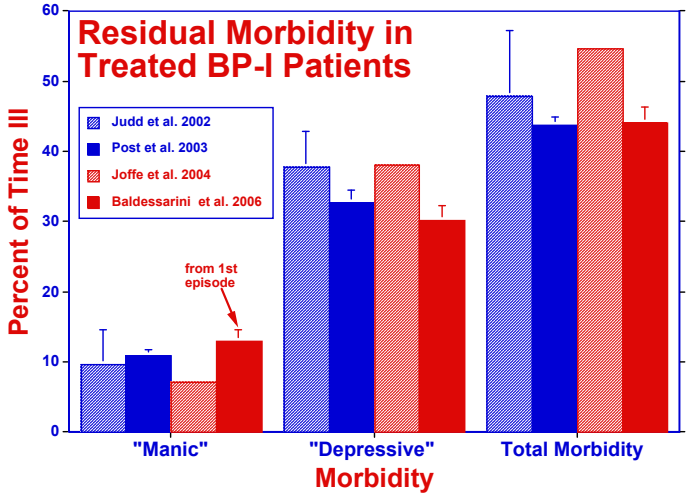


Initial prescriptions for 7760 US bipolar disorder patients

Drug Class	% of Total
Antidepressants	49.8
Modern	47.4
Older (TCAs, MAOIs)	2.42
Mood-stabilizers	24.6
Divalproex sodium	8.31
Other anticonvulsants	8.84
Lithium salts	7.49
Sedative-anxiolytics	14.8
Antipsychotics	10.7
Modern agents	10.1
Older neuroleptics	0.6

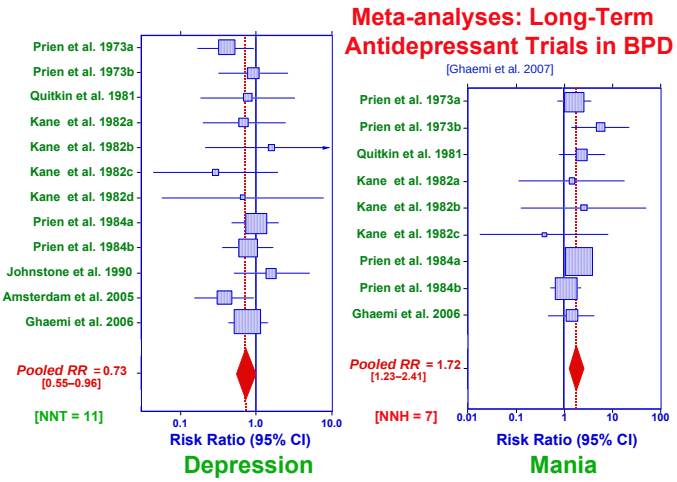
Based on MarketScan pharmacy data, 2003–2004.
Baldessarini et al.: Psychiatr Serv 2007; 58: 85–91.

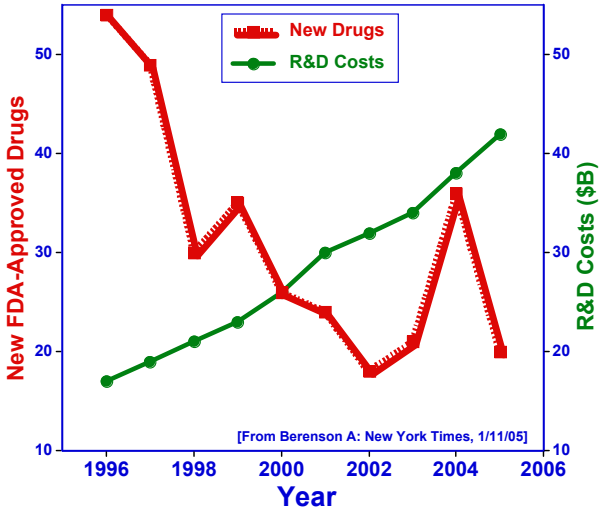




Treatments for bipolar depression

Agent	FDA-Approved Indications
Older Antidepressants	None (MDD only)
Modern Antidepressants	None (MDD only)
Lithium salts	Long-term: BPD "recurrences"
Divalproex	None (antimanic)
Carbamazpine	None (antimanic)
Lamotrigine	Long-term (minimally antimanic)
Olanzapine-fluoxetine	Short-term: BP depression
Quetiapine	Short-term: BP depression (& mania)





Recent "innovations" in psychopharmacology

Metabolites
- Risperidone vs. 9-OH-Risperidone (Paliperidone/Invega®)
- Clozapine vs. Norclozapine

Enantiomers
- Citalopram: *R,S* (Celexa®) vs. *S* (Lexapro®)
- Methylphendate: *d,l* (Ritalin) vs. *d* (Focalin®)
- Modafinil: *d,l* (Provigil®) vs. *l* vs. *d* (in development)

Delivery
- Selegiline: tablets (Eldepryl®) vs. patch (Emsam®)
- Loxapine: tablets (Loxitane®) vs. inhaler (in development)

Names/Indications
- Fluoxetine: Prozac® vs. Serafem®
- Bupropion: Wellbutrin® vs. Zyban®

Into the new millenium

- **Empiricism lives—absent all but a descriptive nosology**
  (It's hard to find a cure without a cause)
- **Blurring of indication boundaries**
  (surrpising breadth of success: "anticonvulsants" "antidepressants, "antipsychotics")
- **Need for better clinical measures & trials designs**
  (weak/narrow rating scales, carry-over & discontinuation artifacts, LOCF artifacts: differential dropouts & long-term artifacts abound)
- **Missed (or avoided?) opportunities**
  (mortality/suicide, kids, the elderly, brain injury & degenerations)
- **Non-pharmacological therapies**
  (man does not live by pills alone; cost-effective psychosocial methods lag in development, testing, financial support)
- **Dumbing-down of psychiatry**
  (cookbook diagnosis+pills, allopathic compulsion, mismanaged care: priority distortion when the bottom-line reigns supreme)
- **Rational medicine & algorithms**
  (good ideas: let's see the data!)

Conclusions:
Current Status of Psychopharmacology

- Many agents are available for most psychiatric disorders; most are reasonably effective & quite safe
- Most psychiatric disorders are recurrent/chronic & require long-term treatments
- Design & interpretation of long-term trials: *major* challenges
- All psychotropics have major limitations in effectiveness, tolerability, & long-term adherence
- Innovation in psychotropics is limited & evidently slowing
- Modern practice has become dominated by simplistic assessment & over-valued, partially-effective medicines