UNIVERSITY OF CALGARY
FACULTY OF MEDICINE

Alberta Health Services
Calgary Health Region

Outcomes of Long Term Medications

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THE MATHISON CENTRE
for MENTAL HEALTH RESEARCH & EDUCATION

HOTCHKISS BRAIN INSTITUTE

Disclaimer

I have received honoraria, travel support and / or grant support from the following pharmaceutical companies:

- Amgen
- AstraZeneca
- BMS
- Boehringer-Ingelheim
- Eli Lilly
- Forum (EnVivo)
- Janssen
- Lundbeck
- Novartis
- Otsuka
- Pfizer
- Purdue
- Roche
- Sanofi Aventis
- Sunovion
- Valeant


57
ADT

Questions

- Are medications effective for psychiatric disorders?
- Do all patients with psychiatric disorders benefit from medications?
- Can all psychiatric disorders be treated with medications?
- Have pharmacological interventions changed the long-term course of psychiatric disorders?

Psychotropic agents pre 1950

- Opium
- Bromides
- Barbiturates
- Hyoscine
- Paraldehyde
- Benzedrine
- Amphetamine
- Thyroxine

Non-pharmacological treatment of psychosis pre 1950

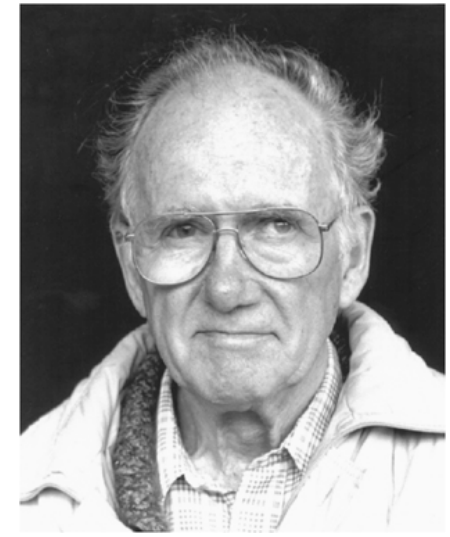
- Physical restraints
- Hydrotherapy
- Insulin coma therapy
- Chemical and electrical shock treatment
- Lobotomy / Leucotomy
- Focus sanitation (‘Eliminate the perils of pus infection’) (dental extraction, colectomy, hysterectomy)

Lithium

Alkali metal

John Cade

"I believe the brain, like any other organ, can get sick and it can also heal."



Mogens Schou

Introduction of chlorpromazine

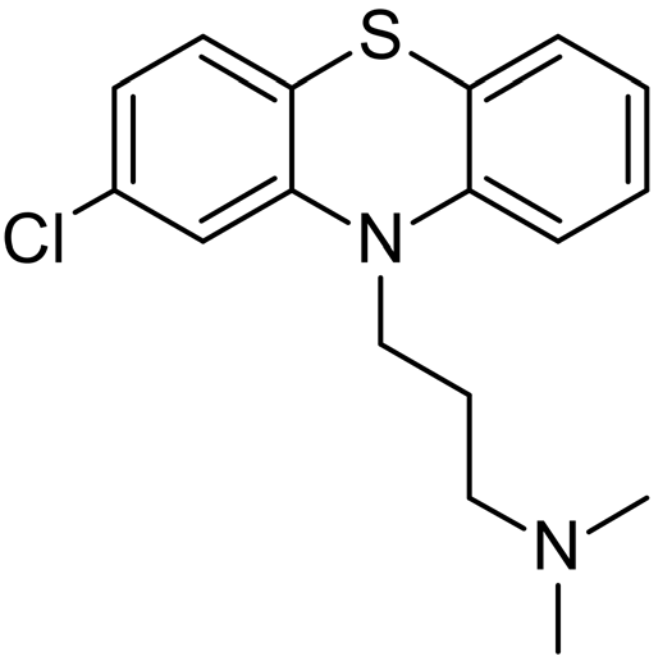
- Reserpine as the first antipsychotic
  Cave depression and suicide

- Cholorpromazine as an antihistamine
  used in anesthesia with unexpected
  psychiatric properties

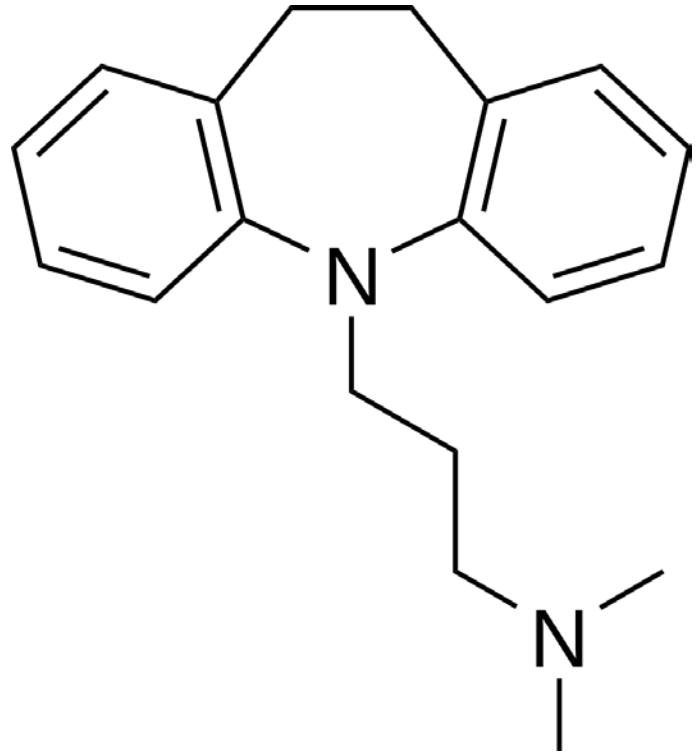
- 1952 first use in schizophrenia by
  Jean Delay and Pierre Deniker in
  Paris

- Addditional phenothiazines and
  butyrophenones synthesized in the 50ies

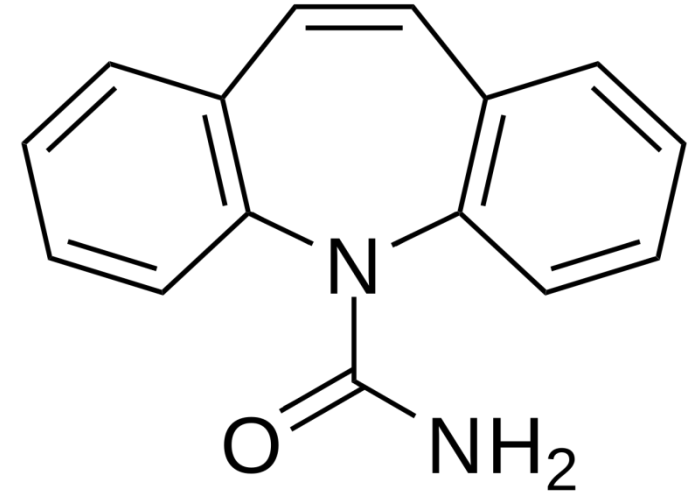
Pierre Deniker



Chlorpromazine

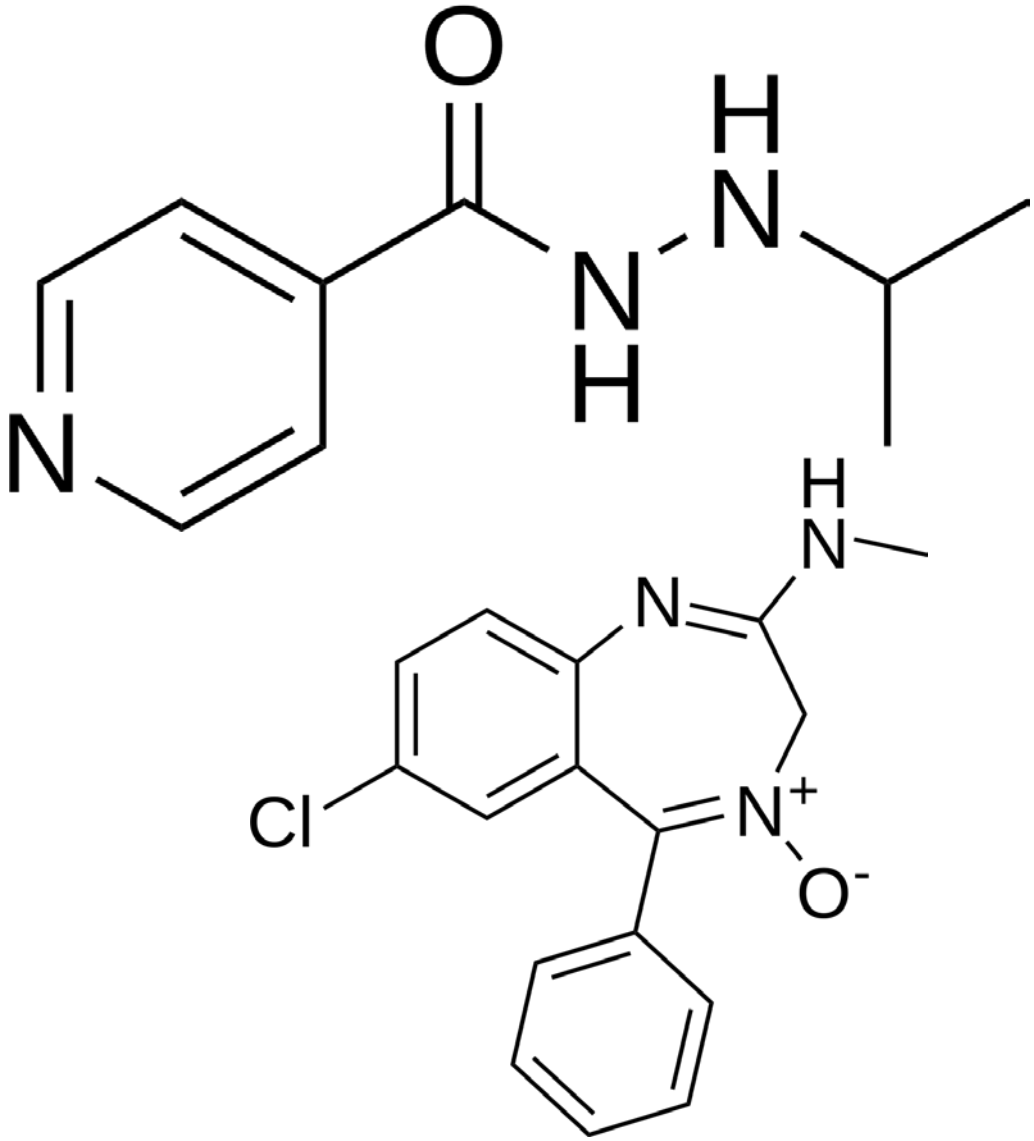


Imipramine



Carbamazepine

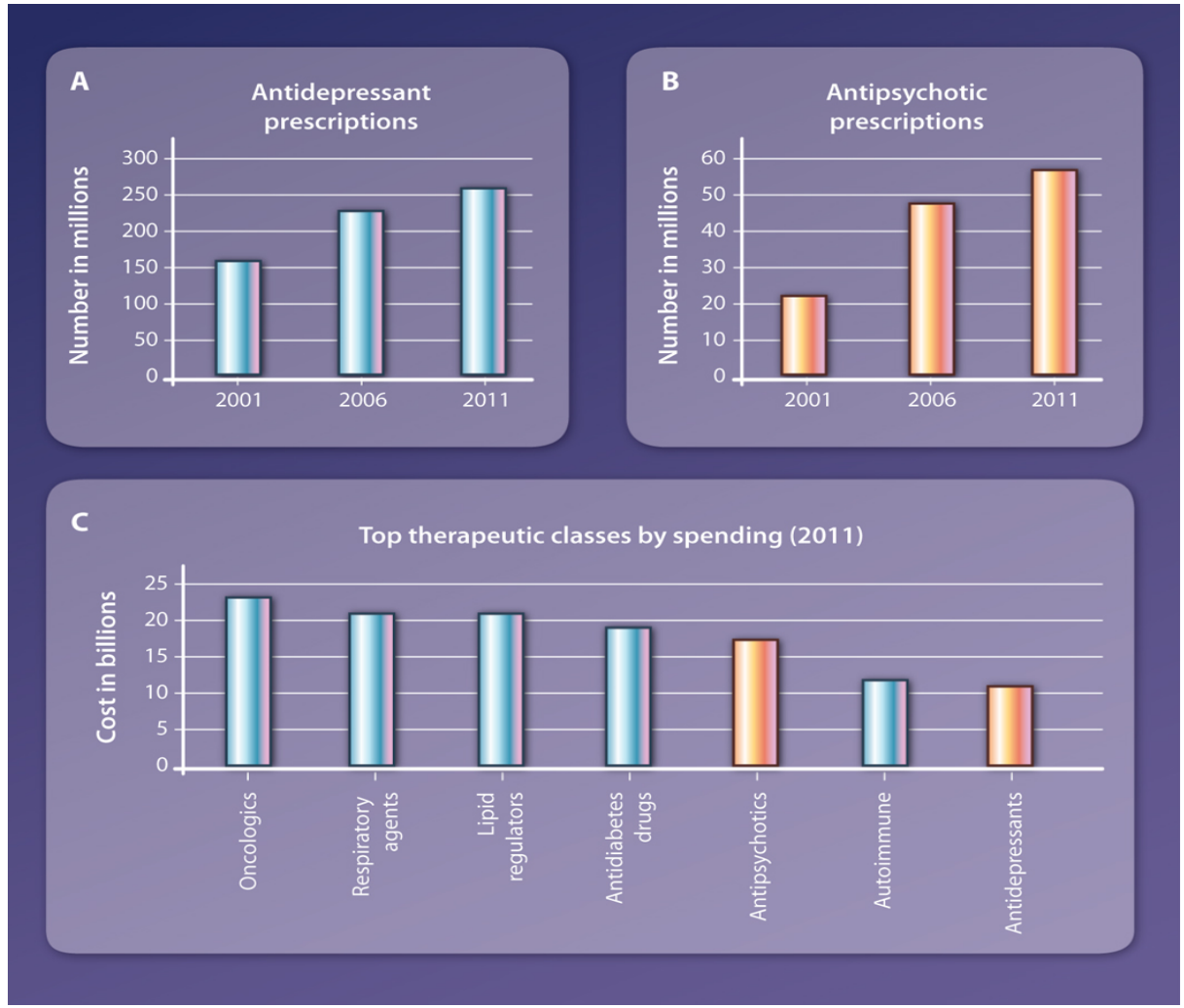
Other psychotropic agents



Iproniazid
Originally developed as a tuberculostaticum
Antidepressant (MAOI) effects discovered in 1952

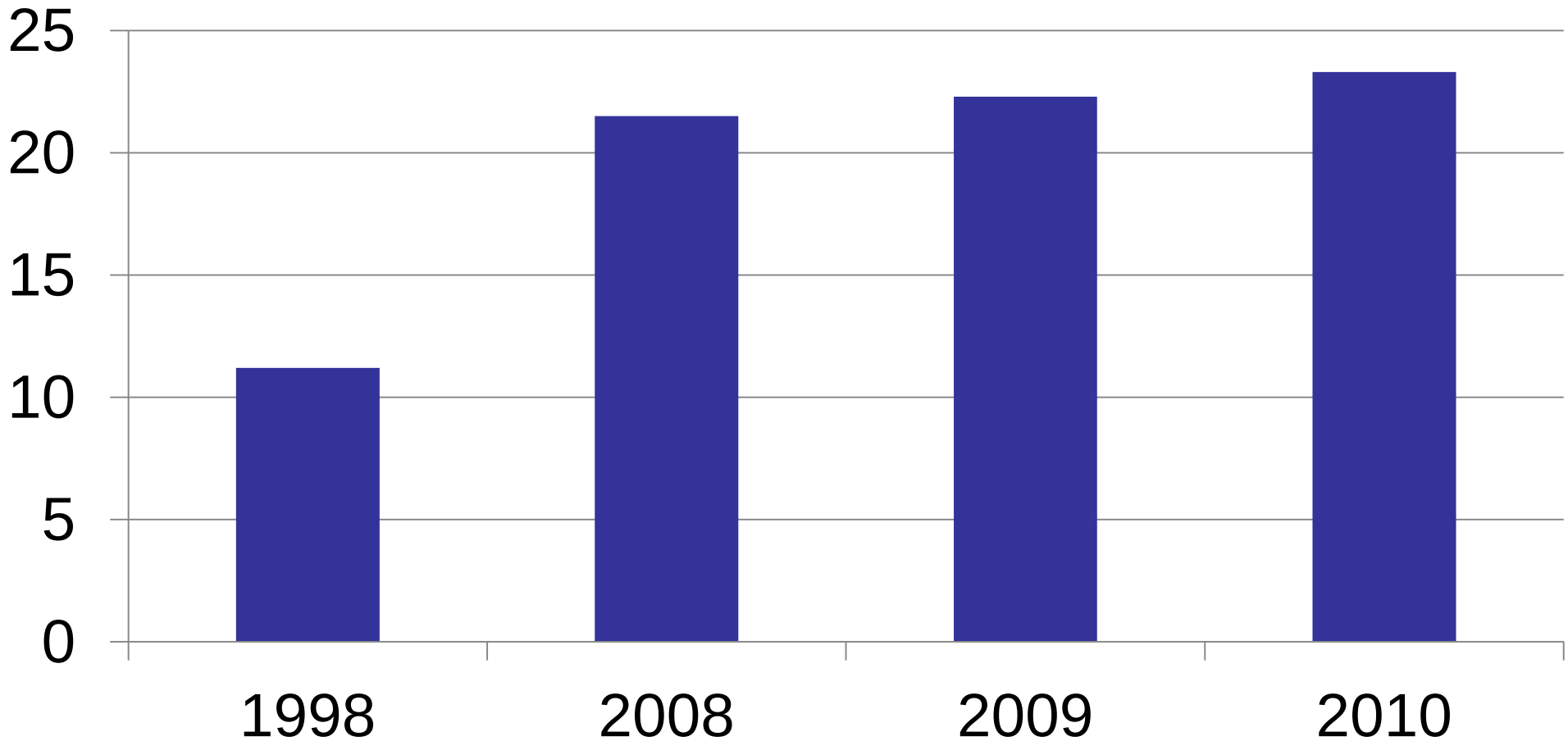
Chlordiazepoxide
First benzodiazepine introduced in 1960

Fig. 1. The growth of psychiatric medications.



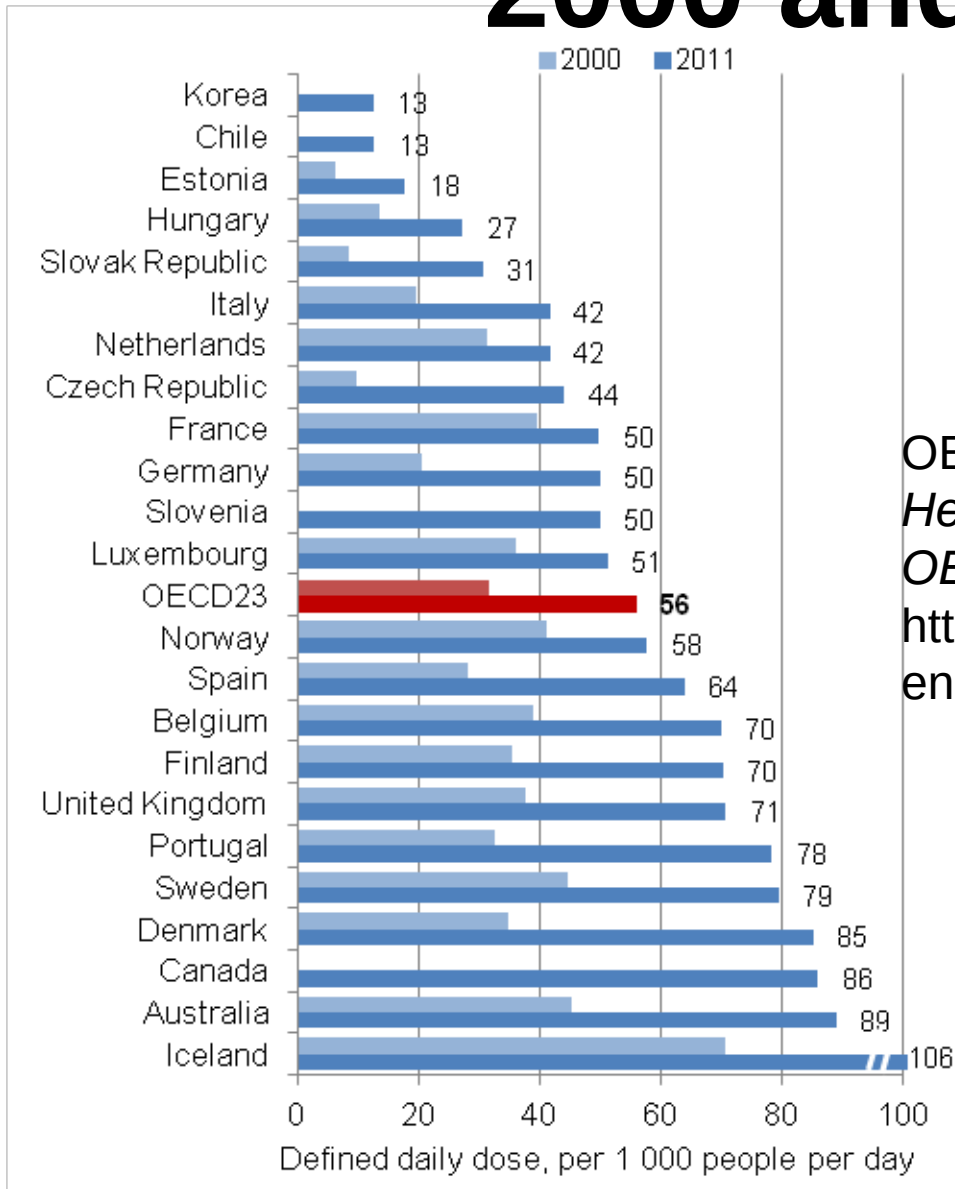
T. R. Insel Sci Transl Med 2012;4:155ps19

Antidepressant Use in United States (Million Users)



Source: Behavioral Health, United States, 2012
SAMHSA (Substance abuse and Mental Health Services Administration)

Antidepressant Consumption, 2000 and 2011



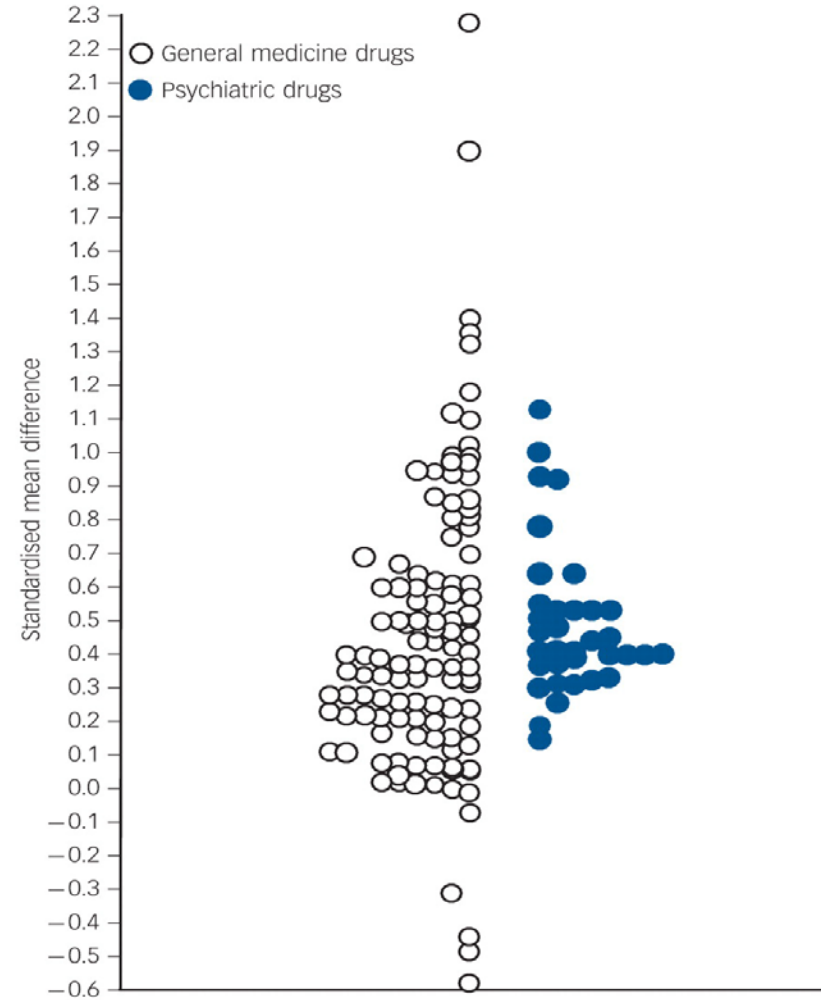
OECD (2013), "Pharmaceutical consumption", in *Health at a Glance 2013: OECD Indicators, OECD Publishing.* http://dx.doi.org/10.1787/health_glance-2013-41-en

Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses

94 meta-analyses
(48 drugs in 20 medical diseases, 16 drugs in 8 psychiatric disorders)

Psychiatric drugs were not generally less efficacious than other drugs

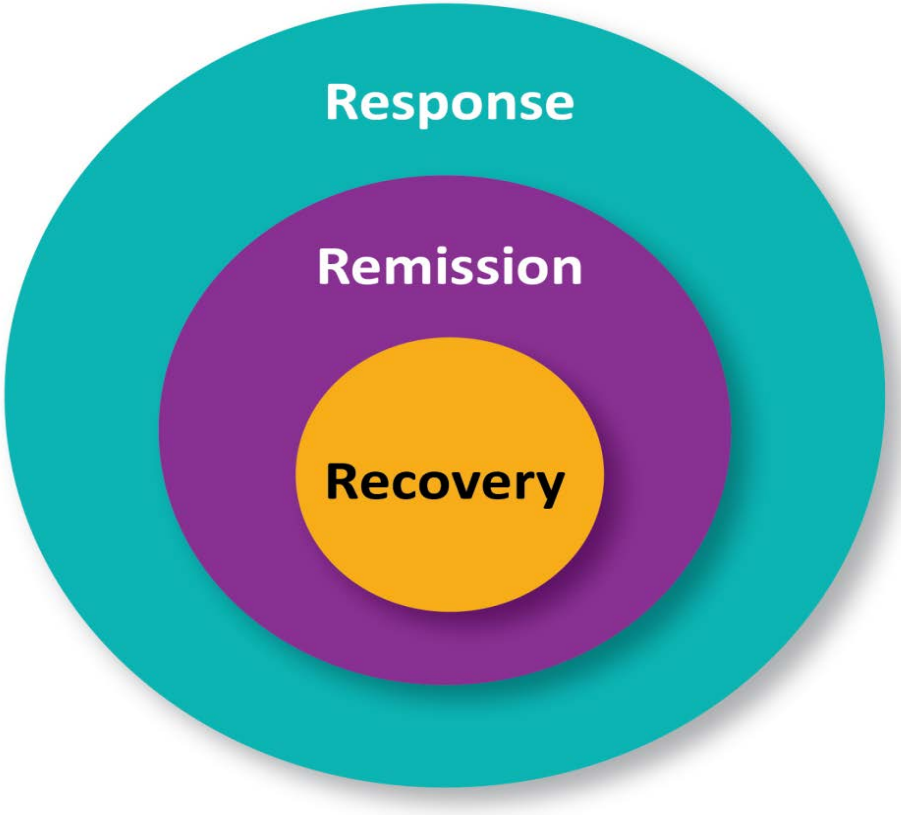
Summary of effect sizes.



Leucht S et al. BJP 2012;200:97-106

THE BRITISH JOURNAL OF PSYCHIATRY

Gap in Levels of Outcome: *A Challenge?*



- **Response:** Percentage decrease in symptoms
- **Remission (APA consensus):** SAPS-SANS global rating 2 or less or PANSS item ratings of 3 or less
- **Recovery:** Independent functioning (work, school, social relationships, independent living); requiring minimal or no support (societal perspective) and, personal sense of well being (personal perspective)

Andreasen NC, *et al. Am J Psychiatry.* 2005;162(3):441–449.

	Number of studies included	Drug group	Control group	Mean study duration* (months)	Risk ratio (95% CI)	Absolute difference (95% CI)	NNTB/H (95% CI)
Relapse 7–12 months	24	392/1465 (27%)	773/1204 (64%)	11	0·40 (0·33 to 0·49)	−0·39 (−0·46 to −0·32)	3 (2 to 3)
Relapse independent of duration	62	744/3395 (22%)	1718/2997 (57%)	9	0·35 (0·29 to 0·41)	−0·38 (−0·43 to −0·33)	3 (2 to 3)
Participants readmitted to hospital	16	112/1132 (10%)	245/958 (26%)	13	0·38 (0·27 to 0·55)	−0·19 (−0·27 to −0·11)	5 (4 to 9)
Dropout for any reason	57	802/2642 (30%)	1130/2076 (54%)	9	0·53 (0·46 to 0·61)	−0·24 (−0·30 to −0·17)	4 (3 to 6)
Dropout because of inefficacy	46	412/2539 (16%)	830/2007 (41%)	8	0·37 (0·31 to 0·44)	−0·27 (−0·34 to −0·19)	4 (3 to 5)
Participants unimproved/worse	14	614/880 (70%)	569/644 (88%)	5	0·73 (0·64 to 0·84)	−0·25 (0·35 to 0·14)	4 (3 to 7)
Violent/aggressive behaviour	5	9/403 (2%)	34/277 (12%)	8	0·27 (0·15 to 0·52)	−0·09 (−0·17 to −0·01)	11 (6 to 100)
Participants employed	2	63/130 (48%)	65/129 (50%)	11	0·96 (0·75 to 1·23)	−0·02 (−0·14 to 0·10)	50 (H7 to B10)†
Death (any)	14	5/1240 (<1%)	7/1116 (1%)	7	0·77 (0·28 to 2·11)	0·00 (−0·01 to 0·00)	∞
Suicide	8	0/1021	2/920 (<1%)	6	0·34 (0·04 to 3·28)	0·00 (−0·01 to 0·00)	∞
Death from natural causes	14	5/1272 (1%)	3/1129 (<1%)	7	1·24 (0·39 to 3·97)	0·00 (0·00 to 0·01)	∞
Dropout because of AE	43	129/2437 (5%)	78/1896 (4%)	8	1·16 (0·70 to 1·91)	0·00 (−0·01 to 0·02)	∞
At least one AE	10	575/1188 (48%)	450/996 (45%)	7	1·01 (0·87 to 1·18)	0·01 (−0·06 to 0·08)	100 (H17 to B13)†
At least one MD	22	304/1901 (16%)	134/1510 (9%)	7	1·55 (1·25 to 1·93)	0·06 (0·03 to 0·10)	17 (10 to 33)
Dyskinesia	13	18/1051 (2%)	37/769 (5%)	9	0·52 (0·28 to 0·97)	−0·01 (−0·02 to 0·01)	100 (H50 to B100)†
Use of antiparkinsonian medication	7	182/748 (24%)	90/569 (16%)	7	1·40 (1·03 to 1·89)	0·09 (0·02 to 0·16)	11 (6 to 50)
Sedation	10	158/1174 (13%)	85/972 (9%)	6	1·50 (1·22 to 1·84)	0·05 (0·00 to 0·10)	20 (B=∞ to H10)†
Weight gain	10	128/1231 (10%)	61/1090 (6%)	7	2·07 (2·31 to 3·25)	0·05 (0·03 to 0·07)	20 (14 to 33)

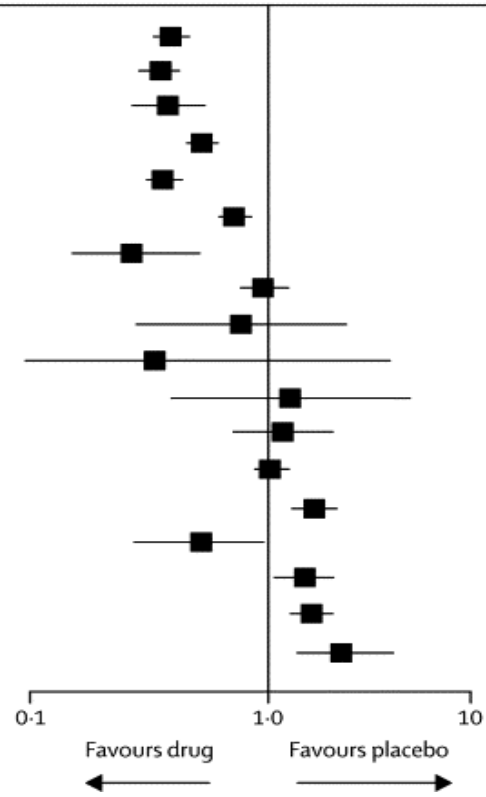


Figure 1 Summary of pooled results Data are n/N (%) unless otherwise stated. The random effects model by DerSimonian and Laird<ce:cross-ref refid="bib17"> 17 </ce:cross-ref> was used throughout, with weights calculated by the Mantel-Haenszel method. NNT...

Stefan Leucht , Magdolna Tardy , Katja Komossa , Stephan Heres , Werner Kissling , Georgia Salanti , John M Davis

Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis

The Lancet, Volume 379, Issue 9831, 2012, 2063 - 2071

http://dx.doi.org/10.1016/S0140-6736(12)60239-6

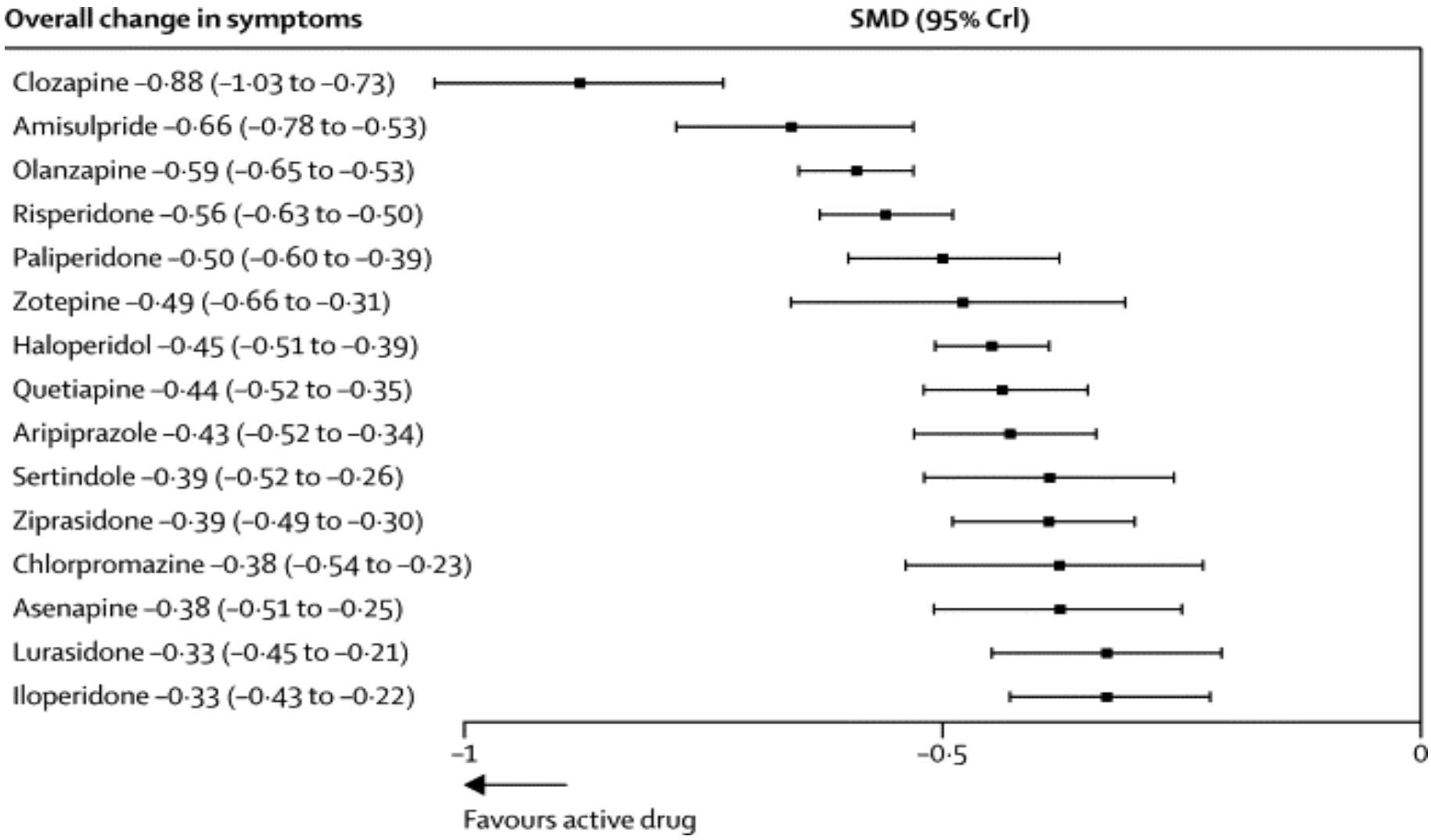


Figure 3 Forest plot for efficacy of antipsychotics drugs compared with placebo Treatments are ranked according to their surface under the cumulative ranking (SUCRA) values (<ce:cross-ref id="cecref10" refid="sec1"> appendix p 98</ce:cross-ref>). SMD=sta...

Stefan Leucht , Andrea Cipriani , Loukia Spineli , Dimitris Mavridis , Deniz Örey , Franziska Richter , Myrto Sam...

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

The Lancet, Volume 382, Issue 9896, 2013, 951 - 962

http://dx.doi.org/10.1016/S0140-6736(13)60733-3

From: **Placebo Response in Antipsychotic Clinical Trials: A Meta-analysis**

JAMA Psychiatry. Published online October 08, 2014. doi:10.1001/jamapsychiatry.2014.1319

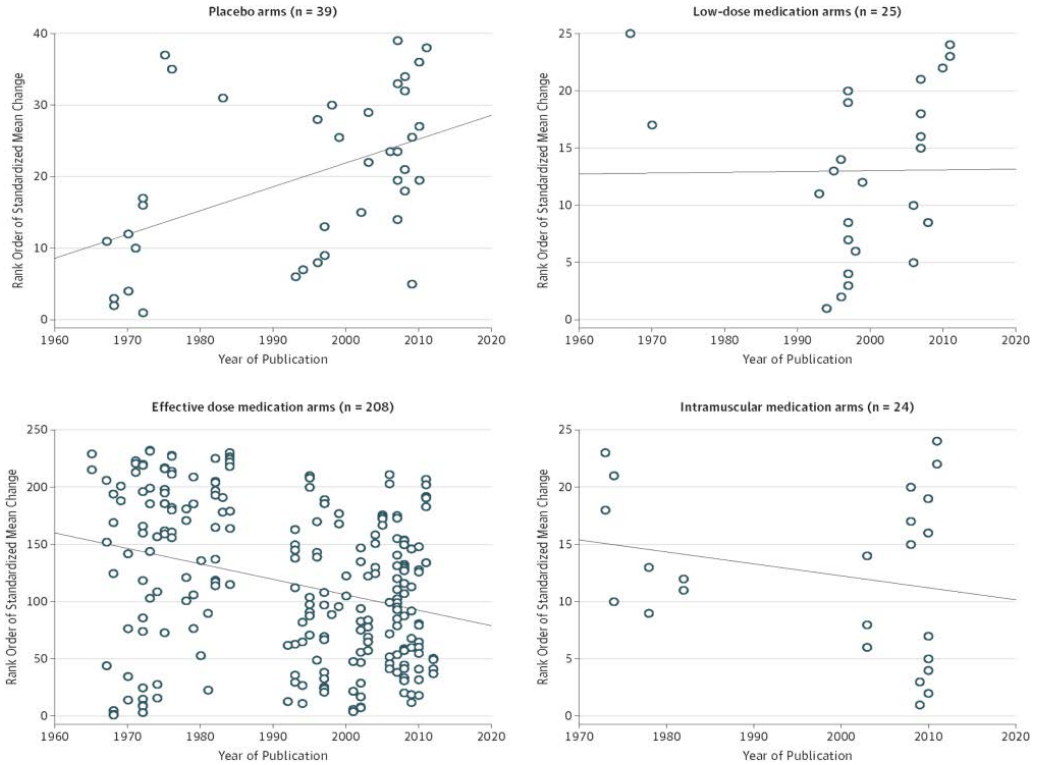


Figure Legend:

Relationship of Standardized Mean Change to Year of Publication for Patients Receiving Placebo or Low-Dose, Effective Dose, or Intramuscular MedicationThe standardized mean change was significantly positively correlated with year of publication for placebo arms (Spearman r = 0.52, n = 39, P = .001) and was significantly negatively correlated with year of publication for the effective dose medication arms (Spearman r = −0.26, n = 208, P < .001), but not for the low-dose medication arms (Spearman r = 0.32, n = 25, P = .12) or the intramuscular medication arms (Spearman r = −0.14, n = 24, P = .53).

THE AMERICAN JOURNAL OF PSYCHIATRY

psychiatryonline

From: Risperidone Nonadherence and Return of Positive Symptoms in the Early Course of Schizophrenia

Am J Psychiatry. 2011;168(3):286-292. doi:10.1176/appi.ajp.2010.09010087

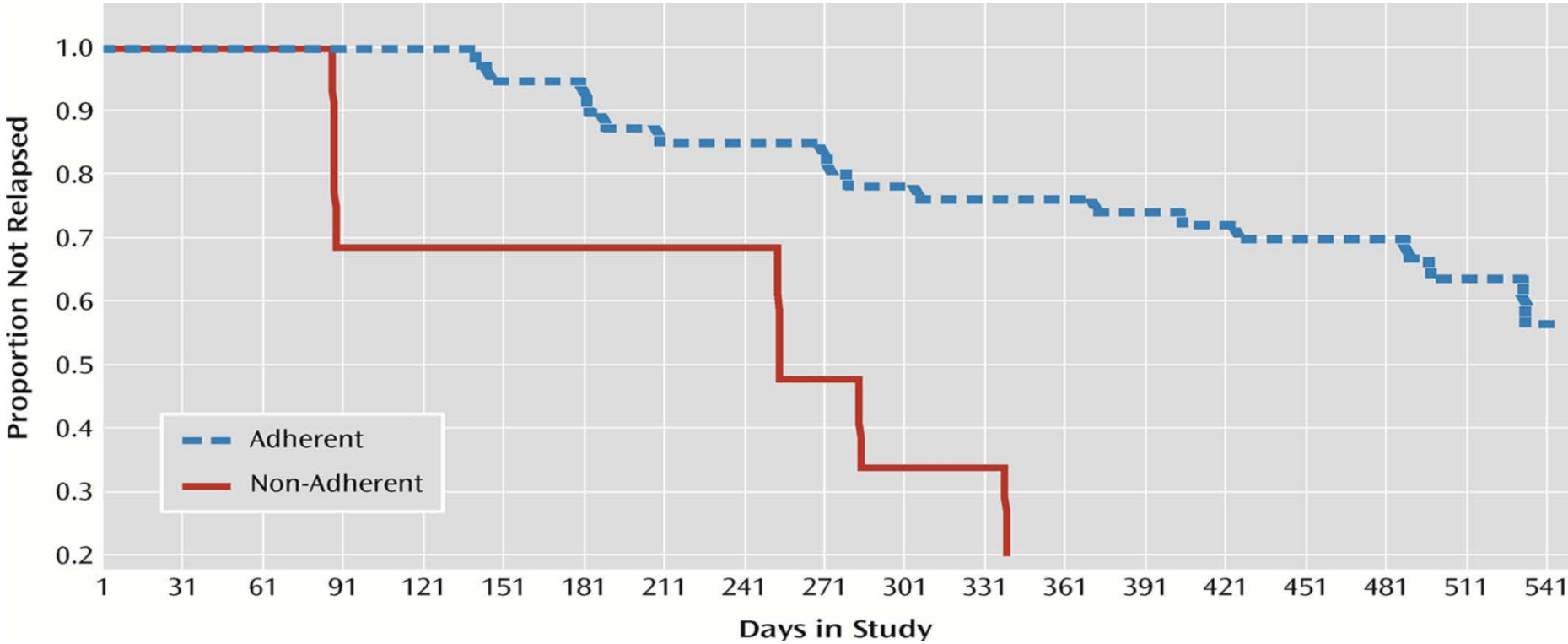
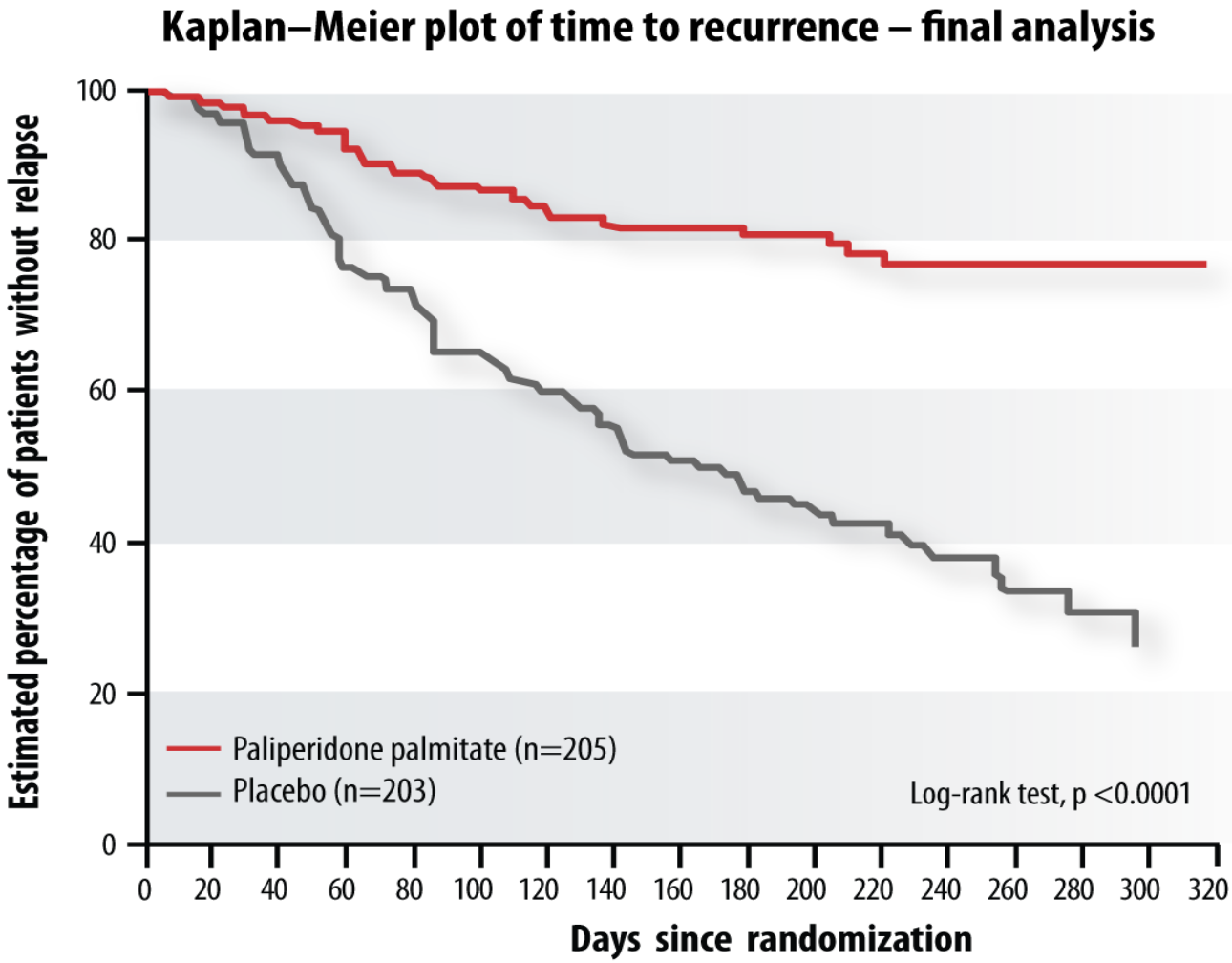


Figure Legend:

Proportion of Recent-Onset Schizophrenia Patients Without Psychotic Exacerbation or Relapse as a Function of Medication Adherence or Nonadherence Status (N=49)[aa] Data are based on whether the participant had a period of moderate or greater nonadherence.

Time to Relapse Compared with Placebo



CI, confidence interval; BMI, body mass index

- Final analysis results for time to relapse were consistent with the interim analysis ($p<0.0001$)
- The hazard ratio (placebo/paliperidone palmitate) was 3.60 (95% CI: 2.45, 5.28)
- The efficacy of paliperidone palmitate with regard to time to relapse was consistent across all subgroups:
  - Age
  - BMI, sex
  - Geographic region

From: **Relapse of Major Depression During Pregnancy in Women Who Maintain or Discontinue Antidepressant Treatment**

JAMA. 2006;295(5):499-507. doi:10.1001/jama.295.5.499

Table 3. Relapse of Major Depression During Pregnancy

Relapse Status	All Women	Medication Status			
		Maintained	Increased	Decreased	Discontinued
No relapse	115 (57.2)	61 (74.4)	11 (55.0)	22 (64.7)	21 (32.3)
Relapse by trimester					
All	86 (42.8)	21 (25.6)	9 (45.0)	12 (35.3)	44 (67.7)
First	44 (51.2)	11 (52.4)	7 (77.8)	5 (41.7)	21 (47.7)
Second	31 (36.0)	9 (42.9)	2 (22.2)	3 (25.0)	19 (43.2)
Third	11 (12.8)	1 (4.8)	0 (0.0)	4 (33.3)	4 (9.1)

201 pregnant females
History of major depression
Euthymic for three months prior to their last menstrual period
Currently or recently receiving antidepressant medication

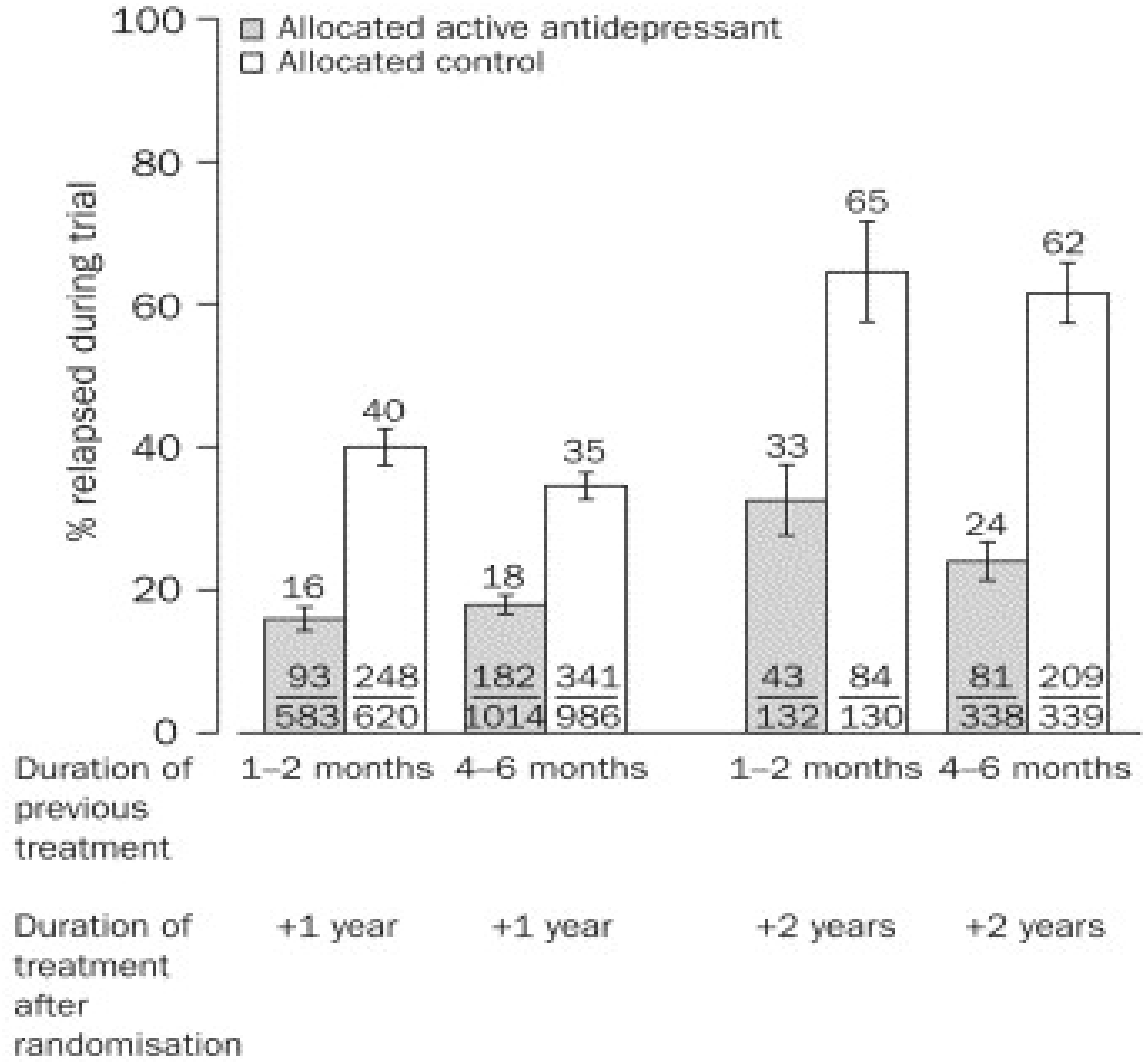


Figure 4 Relapse rates after 1 or 2 years' prolongation of antidepressant treatment in patients already treated for 1–2 or 4–6 months after an acute episode of depression

John R Geddes , Stuart M Carney , Christina Davies , Toshiaki A Furukawa , David J Kupfer , Ellen Frank , Guy M G...

Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review

The Lancet, Volume 361, Issue 9358, 2003, 653 - 661

http://dx.doi.org/10.1016/S0140-6736(03)12599-8

From: **Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy: Long-term Follow-up of a 2-Year Randomized Clinical Trial**

JAMA Psychiatry. 2013;70(9):913-920. doi:10.1001/jamapsychiatry.2013.19

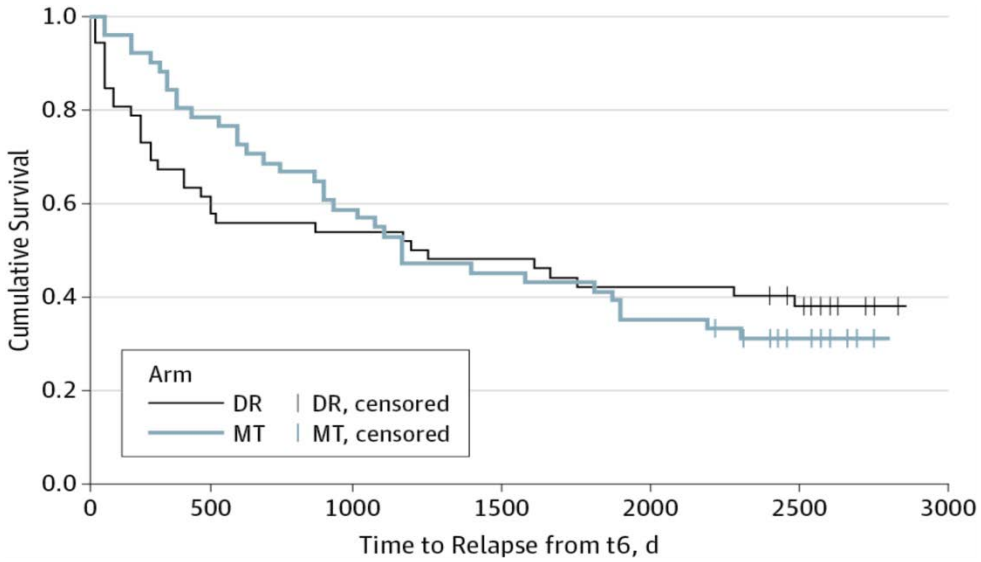


Figure Legend:

Kaplan-Meier Survival AnalysisTime to first relapse after first remission (t6) during 7 years of follow-up in patients assigned to 18 months (547 days) of dose reduction/discontinuation (DR) or maintenance treatment (MT).

From: **Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy: Long-term Follow-up of a 2-Year Randomized Clinical Trial**

JAMA Psychiatry. 2013;70(9):913-920. doi:10.1001/jamapsychiatry.2013.19

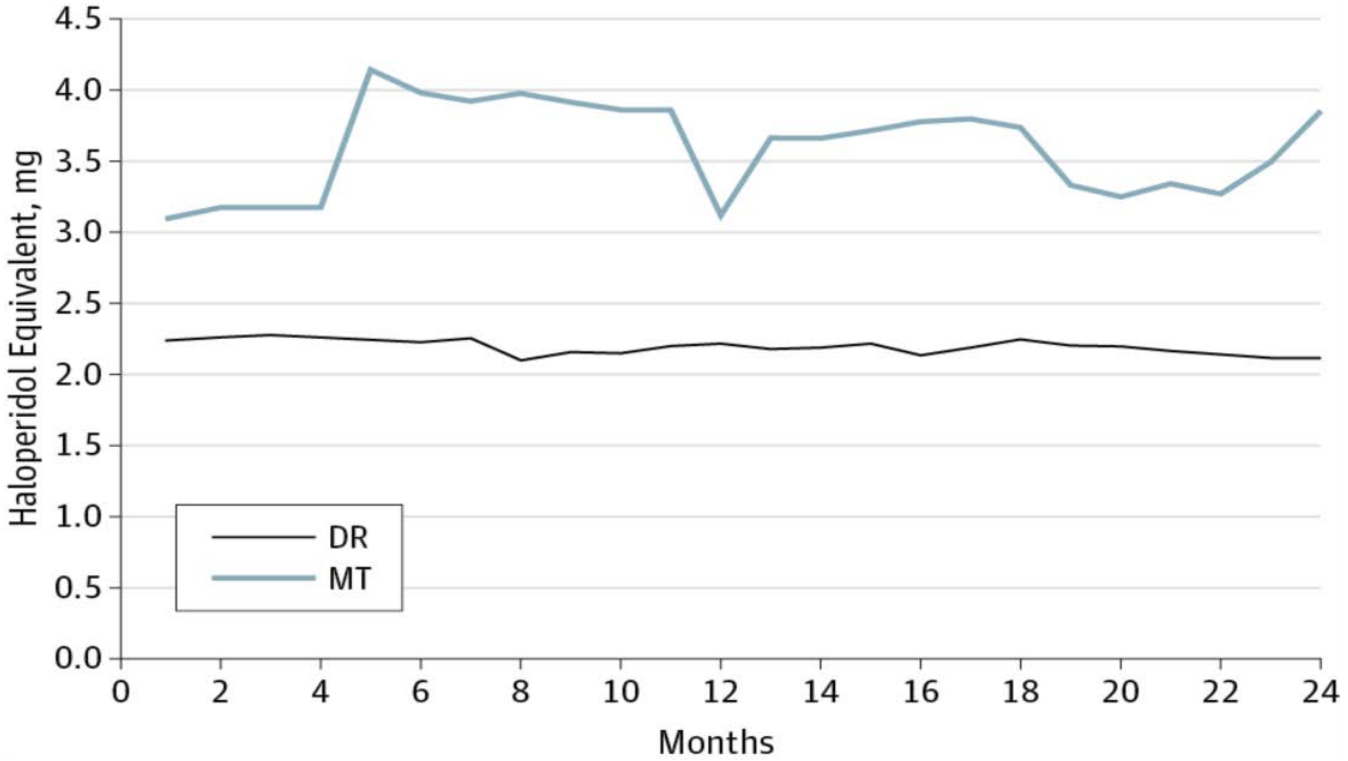


Figure Legend:

Mean Daily Dose in Dose Reduction/Discontinuation (DR) and Maintenance Treatment (MT) During the Last 2 Years of 7-Year Follow-up

From: **Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy: Long-term Follow-up of a 2-Year Randomized Clinical Trial**

JAMA Psychiatry. 2013;70(9):913-920. doi:10.1001/jamapsychiatry.2013.19

Table 2. Recovery, Symptomatic Remission, and Functional Remission After 7 Years of Follow-up

Characteristic	No. (%) DR (n = 52)	MT (n = 51)	Total Sample (n = 103)
Recovery	21 (40.4)	9 (17.6)	30 (29.1)
Remission			
Symptomatic	36 (69.2)	34 (66.7)	70 (68.0)
Functional	24 (46.2)	10 (19.6)	34 (33.0)

Abbreviations: DR, dose reduction/discontinuation; MT, maintenance treatment.

Table Title:

Recovery, Symptomatic Remission, and Functional Remission After 7 Years of Follow-up

Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010

Whiteford et al., Lancet 2013; 382: 1575–86

- Mental and Substance Use Disorders:
  183.900.000 DALYs worldwide
  7.4% of all DALYs (5th overall - 5.4% in 1990)
  0.5% YLL (years of life lost to premature mortality)
  22.9% YLD (years lived with disability) - **highest**
- Depressive Disorders 40.9% of DALYs
- Burden of mental and substance use disorders increased by 37.6% between 1990 and 2010
- Acute schizophrenia highest disability weight of all disorders

More Sobering Facts

- Sustained recovery in less than 14% after a first psychotic episode
- Less than 20% of subjects with schizophrenia are employed in Europe
- Almost 20% of subjects with schizophrenia become homeless during a 1 year follow-up period

Insel, Nature, 2010

Long term outcome in first episode psychosis

- Data from EPPIC in Melbourne, Australia
- Subjects with first episode psychosis
- Median duration of follow-up 7.5 years
- A quarter of subjects had symptomatic remission and social / vocational recovery
- 16.5% had no psychotic relapse
  Short duration of untreated psychosis and rapid response to antipsychotics as predictors

Henry 2010; Alvarez-Jimenez 2011

Prediction of Functional Outcome in Individuals at Clinical High Risk for Psychosis Carrion et al., JAMA Psychiatry 2013

- Poor functional outcomes were not entirely dependent on the development of psychosis. Nonconverters at clinical high risk had poor social outcome (40.3%) and role outcome (45.5%).
- 77 nonconverters, 15 converters
- 35.9% good social and role outcome
  32.6% poor social and role outcome
  47.8% poor social outcome
  48.9% poor role outcome

Questions

- Are medications effective for psychiatric disorders?
- Do all patients with psychiatric disorders benefit from medications?
- Can all psychiatric disorders be treated with medications?
- Have pharmacological interventions changed the long-term course of psychiatric disorders?

Unmet Needs

- Schizophrenia - Negative symptoms
- Schizophrenia – Cognitive dysfunction
- Treatment-refractory mood disorders and anxiety disorders
- Autism
- Eating Disorders
- Substance-use disorders
- Dementia

Thank you
for your attention