

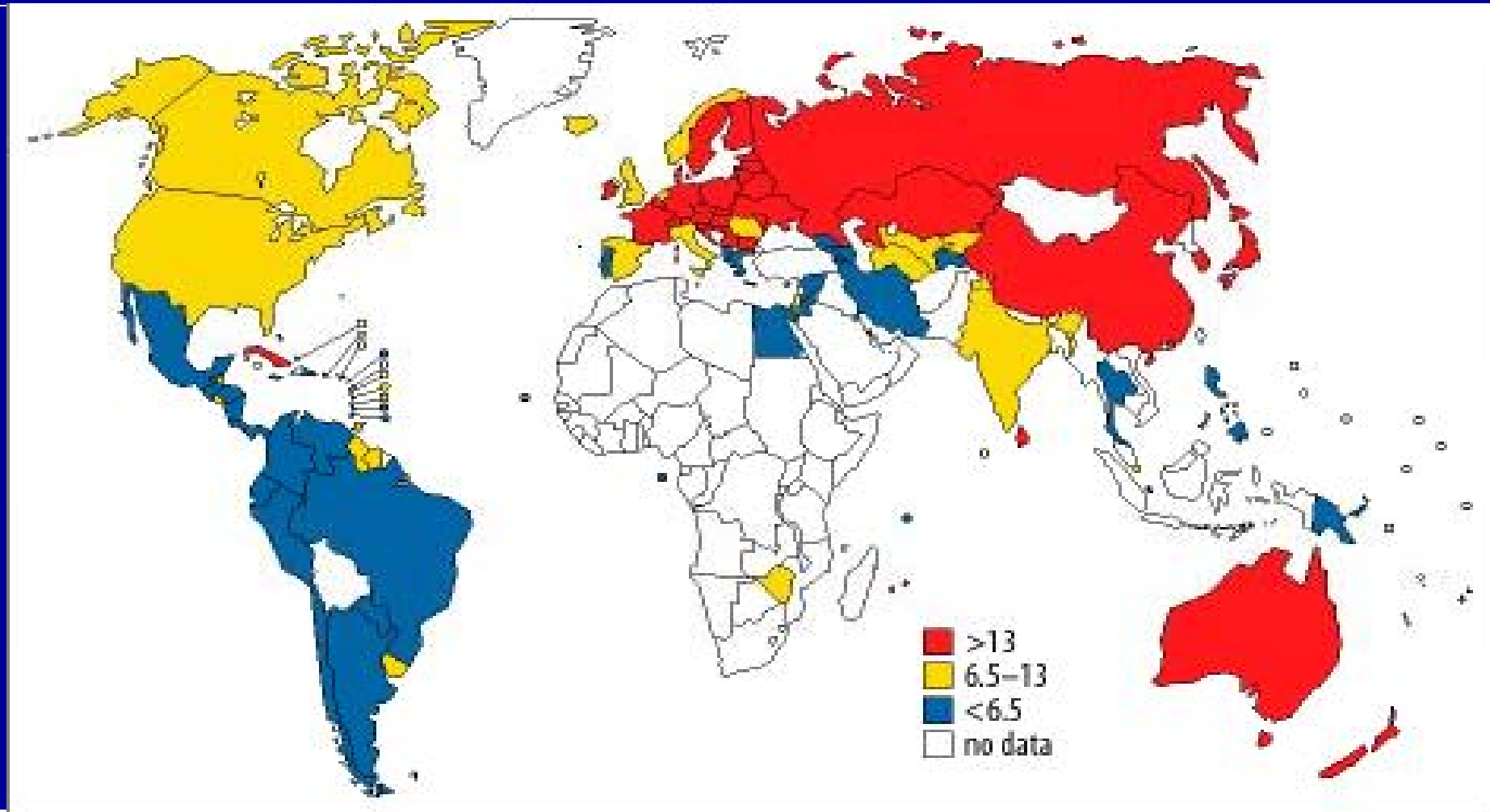
Suicide in Schizophrenia & Affective disorders

March 3, 2010

Istvan Bitter

Department of Psychiatry and Psychotherapy

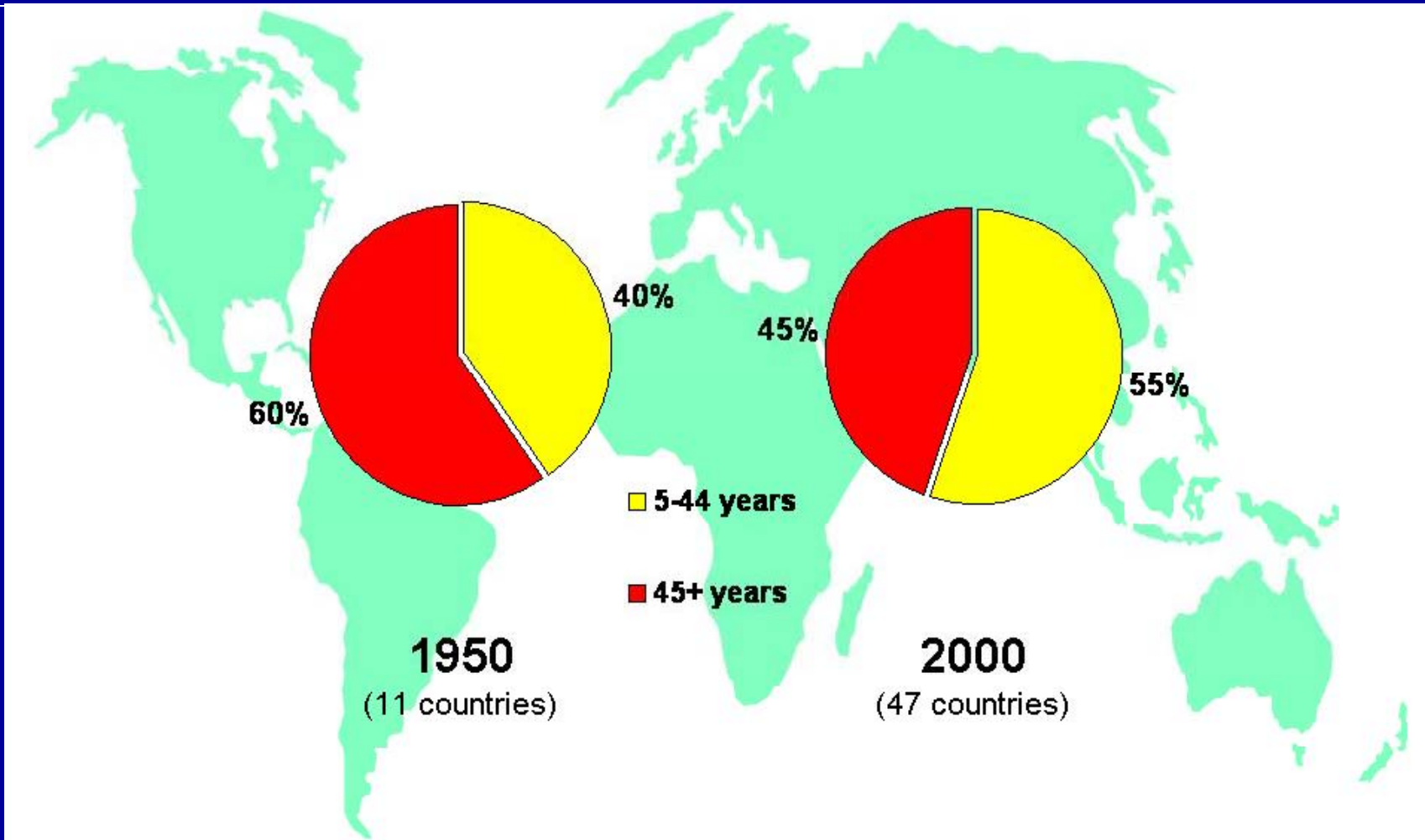
Map of Suicide Rates



(per 100,000; most recent year available, March 2002)

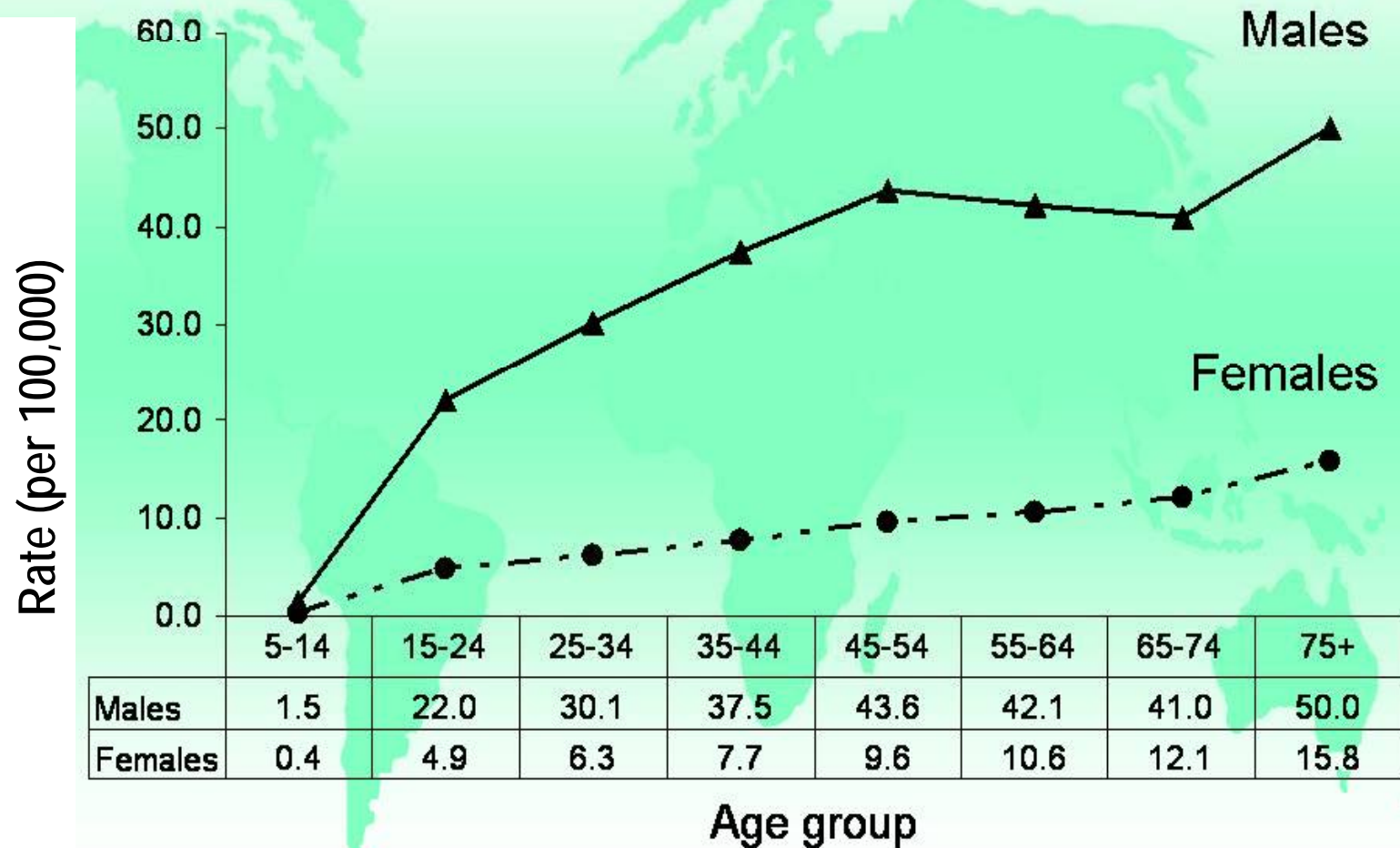
Adapted from: World Health organization. Available at: http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/ Accessed: September, 2005.

Changes in the Age Distribution of Cases of Suicide Between 1950 and 2000



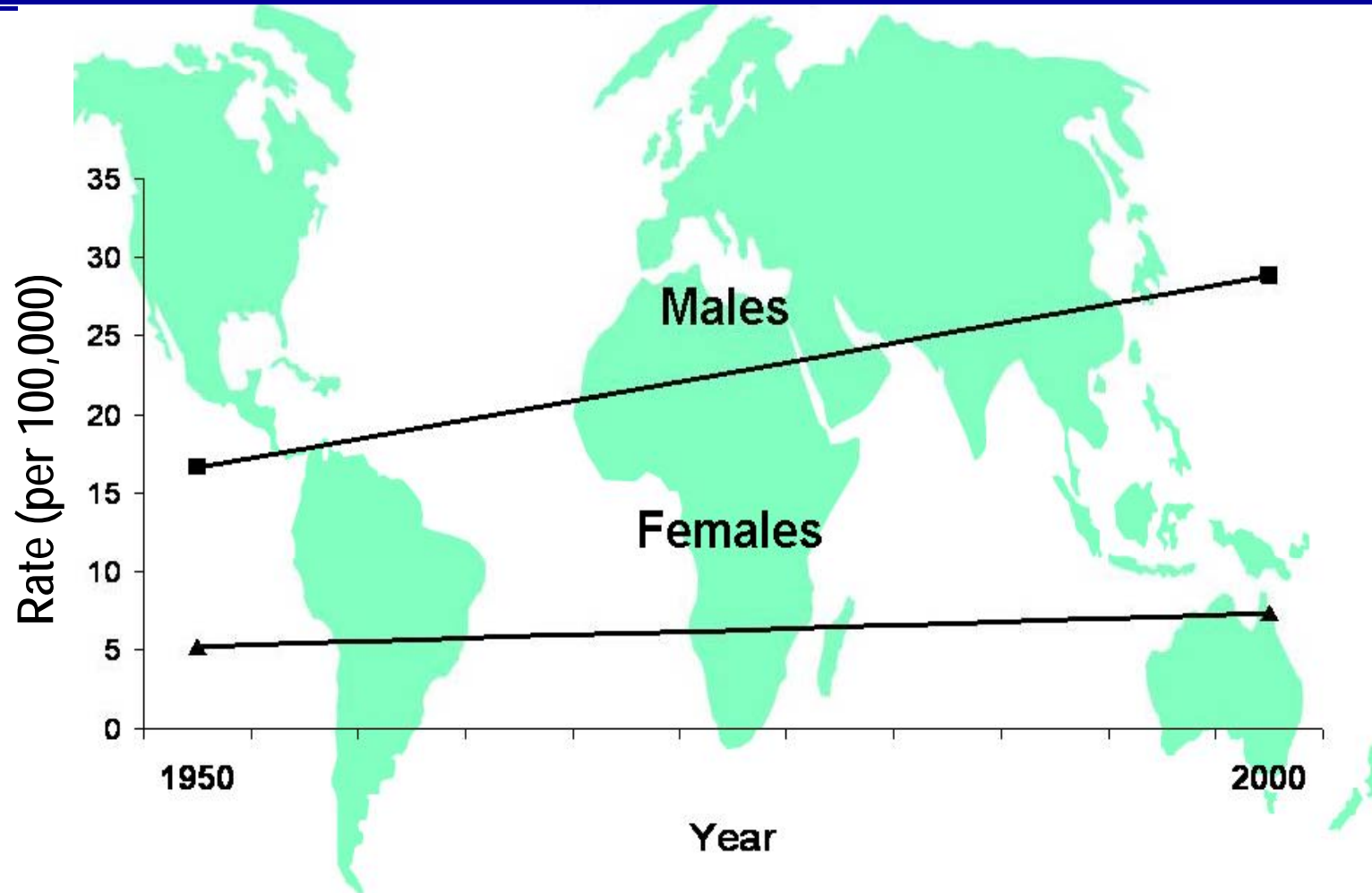
Adapted from: World Health organization. Available at: http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/ Accessed: September, 2005.

Distribution of Suicide Rates by Gender and Age, 2000



Adapted from: World Health organization. Available at: http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/ Accessed: September, 2005.

Evolution of Global Suicide Rates 1950-2000



Adapted from: World Health organization. Available at: http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/ Accessed: September, 2005.

Suicide Rates Per 100,000 Persons Aged 15-19

Country	Year	Males	Females	Total
Germany	2001	8,7	2,4	5,6
Norway	2001	15,3	6,2	10,9
Lithuania	2002	31,2	10,5	21,0

Suicide: Relative Risks in Specific Disorders

Condition	RR
Prior suicide attempt	38.4
Eating disorders	23.1
<i>Bipolar disorder</i>	21.7
<i>Major depression</i>	20.4
Mixed drug abuse	19.2
Dysthymia	12.1
Obsessive-compulsive	11.5
Panic disorder	10.0
<i>Schizophrenia</i>	8.45
Personality disorders	7.08
Alcohol abuse	5.86
Cancer	1.80
General population	1.00

Adapted from: American Psychiatric Association. Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors. 2003;Part A:16, and Busch KA, et al. *J Clin Psychiatry*. 2003 Jan;64(1):14-9.

Suicide

Suicide (self-inflicted death) occurs in all parts of the world. Suicide causes about half of all deaths due to violence. Approximately 1 million persons die each year worldwide from suicide. Suicide is the third leading cause of death among persons aged 15 to 24 years in the United States, following unintentional injuries and homicide. Suicide is often preventable. Warning signs are often present, and individuals who talk about killing themselves must be taken seriously. Mental illness is present in most persons who die by suicide. Treating these mental illnesses can help to decrease the number of deaths by suicide. Suicide affects not only the person who dies but also his or her entire social structure—family, friends, and acquaintances. The May 25, 2005, issue of *JAMA* includes a report of surveys about suicidal thoughts and behaviors in persons living in the United States.

RISK FACTORS FOR SUICIDE

- Depression (especially feeling hopeless)
- **Bipolar illness** (episodes of depression and abnormally elevated moods)
- **Schizophrenia** (a severe mental disorder with disturbances of thinking, mood, and behavior)
- Alcohol and other drug abuse
- Family history of suicide
- Previous suicide attempts
- Childhood abuse
- Chronic physical illness

RESPONDING TO SOMEONE CONSIDERING SUICIDE

FOR MORE INFORMATION

- National Strategy for Suicide Prevention
Life line: 800/273-8255
www.mentalhealth.samhsa.gov/suicideprevention
- American Foundation for Suicide Prevention

Suicide in General Population vs in Persons with Psychiatric Disorder

- Major differences between regions, countries and even within countries in general population suicide rates
- General population risk factors are less predictive of suicide in patients with psychiatric disorders

Slide 9

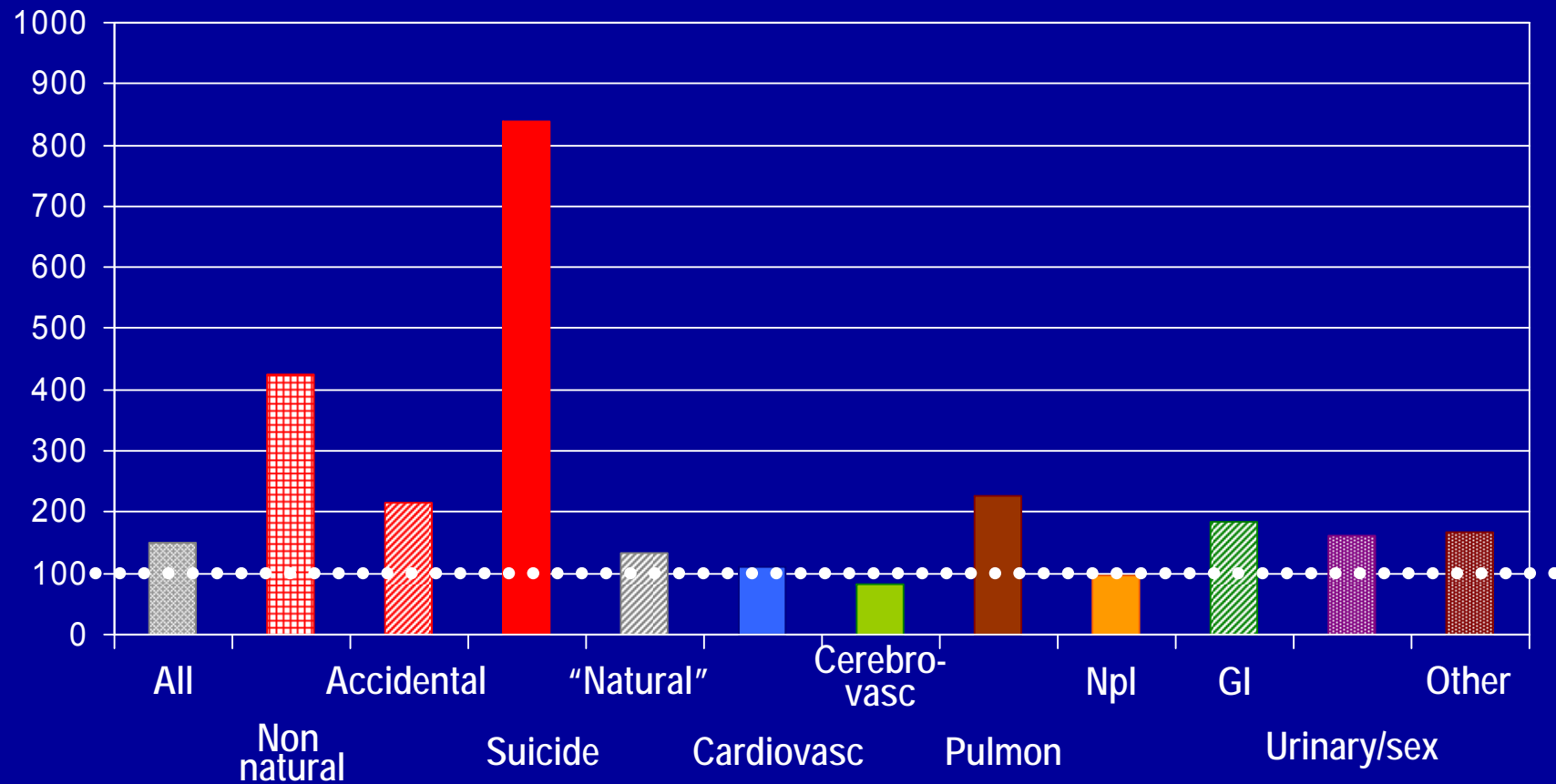
cdv5

Ref to come. Prof Bitter to comment

CdeVries; 2005.09.30.

Mortality in Schizophrenia

Standardized Mortality Ratio



Brown S. *Br J Psychiatry*. 1997; 171: 502-508

Depression in Schizophrenia

- 50-60% of patients suffering from schizophrenia have at least one lifetime depressive episode meeting criteria for major depressive episode
- Victims of suicide with the diagnosis of schizophrenia had higher rates of depressive symptoms and were twice as likely to have depressed mood¹
- Awareness levels of illness are positively related to suicide risk, but there is suggestion that such affects are mediated by depression or hopelessness levels and increase in awareness related to treatments decreased the risk of suicide events²

1. Kelly DL, et al. *J Psychiatr Res.* 2004;38:531-536.

2. BourgeoisM, et al. *Am J Psychiatry.* 2004;161:1494-1496.

Predictors of Suicidal Risk in Schizophrenia and Schizoaffective Disorders

- Diagnosis of schizoaffective disorder
- History or current use (baseline) of alcohol or substance abuse
- Cigarette smoking (baseline)
- Number of lifetime suicide attempts
- Number of hospitalizations (previous 36 months)
- Higher baseline anxiety scores (Covi Anxiety scale)
- Higher baseline depression scores (Calgary Depression Scale)
- Baseline severity of Parkinsonism

International Suicide Treatment Prevention Trial (InterSept): Clozapine vs Olanzapine

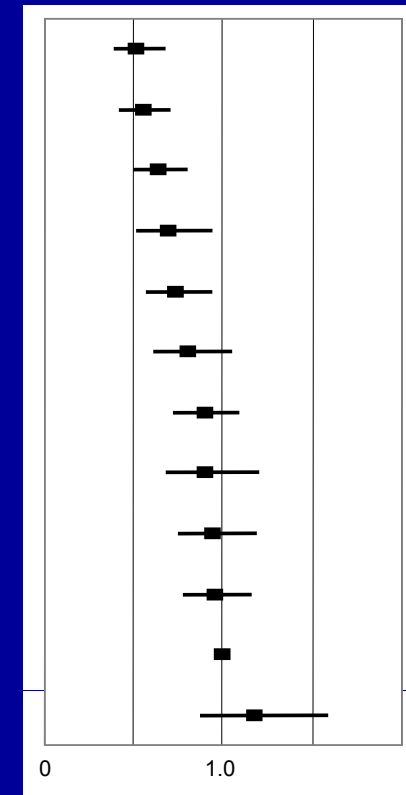
- Suicidal behavior was significantly less in patients treated with clozapine (n=490) vs olanzapine (n=490); fewer clozapine patients attempted suicide (34 vs 55; $P=0.03$)
- No difference in suicide death (clozapine=5; olanzapine=3)

From the Finnish Cohort Study

Relative risk (RR) of re-hospitalization obtained by using medication as time-dependent variable.

RRs have been adjusted with multivariate regression (MVR) using Poisson regression and by including gender, calendar year, age at the onset of follow-up, the number of previous relapses, and the length of the first hospitalization and follow-up period in the model, and also with propensity score (PS) method.

	Number of relapses	Person years	Incidence	Crude RR (95% CI)	MVR Adjusted RR (95% CI)	PS + MVR Adjusted RR (95% CI)
ALL PATIENTS						
Perphenazine depot	53	187	0.28	0.41 (0.29 – 0.59)	0.45 (0.32 – 0.65)	0.51 (0.38 – 0.68)
Clozapine	336	804	0.42	0.61 (0.47 – 0.79)	0.53 (0.41 – 0.69)	0.55 (0.42 – 0.71)
Olanzapine	329	822	0.40	0.59 (0.45 – 0.75)	0.55 (0.43 – 0.72)	0.63 (0.50 – 0.80)
Chlorprothixene	79	146	0.54	0.79 (0.58 – 1.09)	0.83 (0.61 – 1.15)	0.69 (0.51 – 0.94)
Perphenazine oral	155	327	0.47	0.69 (0.58 – 0.82)	0.78 (0.59 – 1.03)	0.73 (0.57 – 0.94)
Thioridazine	115	201	0.57	0.84 (0.63 – 1.12)	0.82 (0.61 – 1.10)	0.80 (0.61 – 1.05)
Mixed or rare	775	1229	0.63	0.92 (0.73 – 1.17)	0.85 (0.67 – 1.08)	0.89 (0.72 – 1.09)
Chlorpromazine	82	127	0.64	0.94 (0.69 – 1.29)	0.97 (0.71 – 1.33)	0.90 (0.67 – 1.20)
Risperidone	343	651	0.53	0.77 (0.60 – 0.99)	0.80 (0.62 – 1.03)	0.94 (0.75 – 1.19)
No medication	2248	3362	0.67	0.98 (0.77 – 1.23)	1.01 (0.80 – 1.27)	0.95 (0.77 – 1.16)
Haloperidol oral	73	107	0.68	1.00 (reference)	1.00 (reference)	1.00 (reference)
Levomepromazine	52	63	0.82	1.21 (0.84 – 1.73)	0.82 (0.58 – 1.18)	1.17 (0.87 – 1.59)



Mortality was markedly elevated in patients not on any medication (adjusted RR 12.3, 95% CI 6.0–24.1), and the risk of suicide was even higher (RR 37.4, 5.1–276).

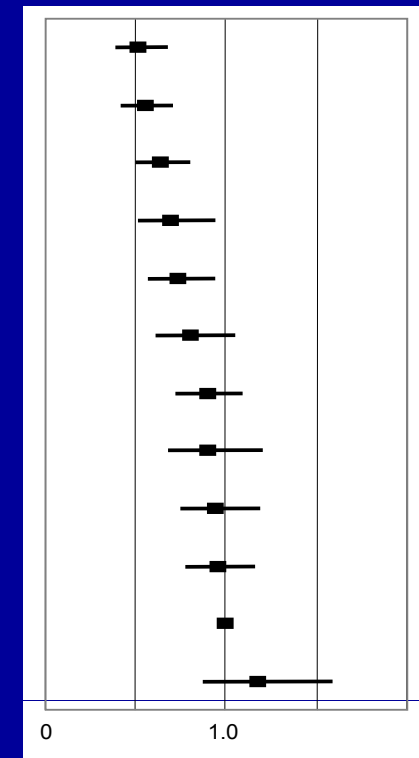
Adapted from: Tiihonen J. Presented at Tallinn. May 19, 2005.

From the Finnish Cohort Study

Relative risk (RR) of re-hospitalization obtained by using medication as time dependent variable.

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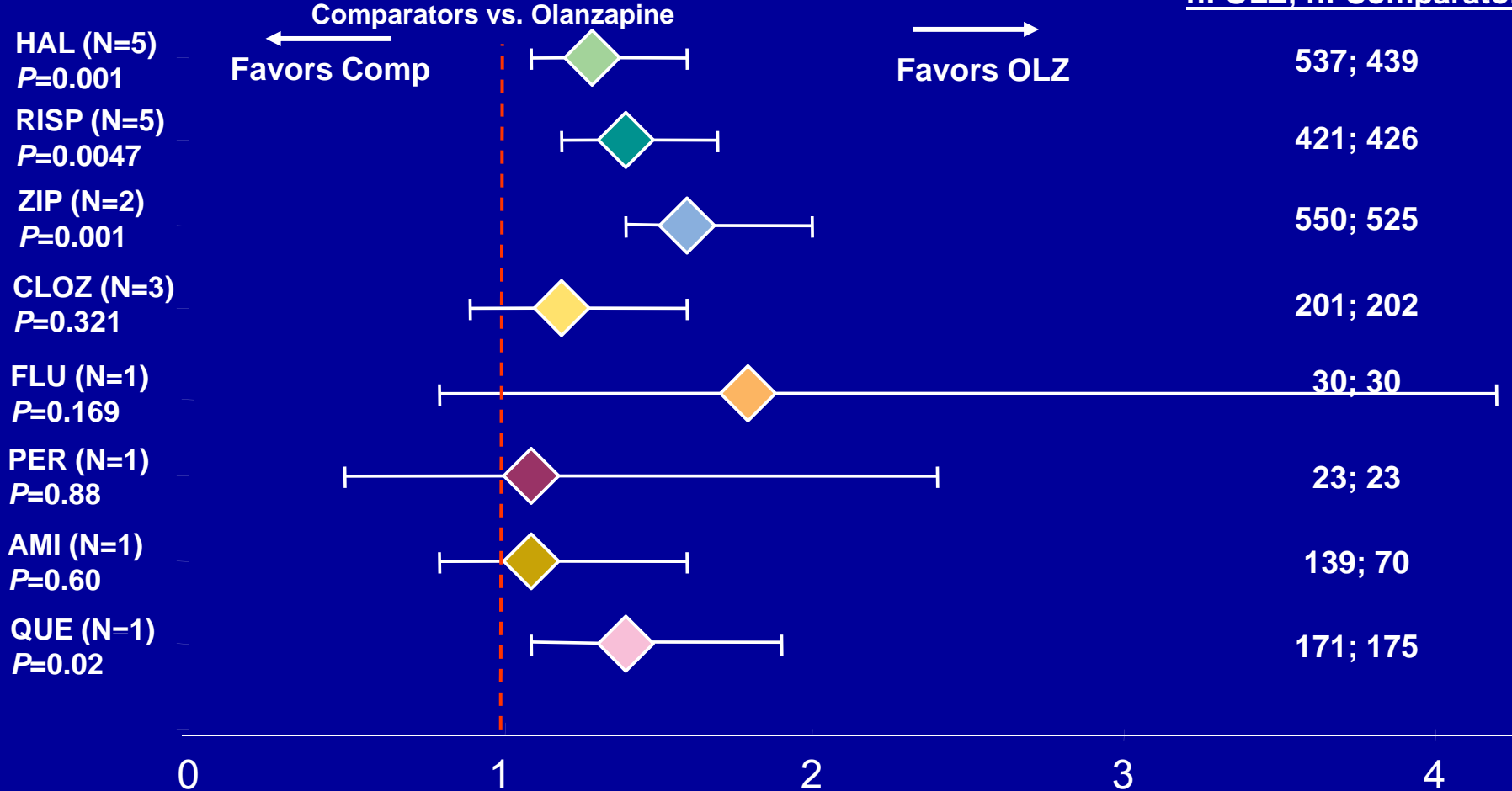


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"Staying on Treatment" From Double Blind Randomized Studies

Hazard Ratios with Confidence Intervals for Discontinuation on Therapy:

n: OLZ; n: Comparator



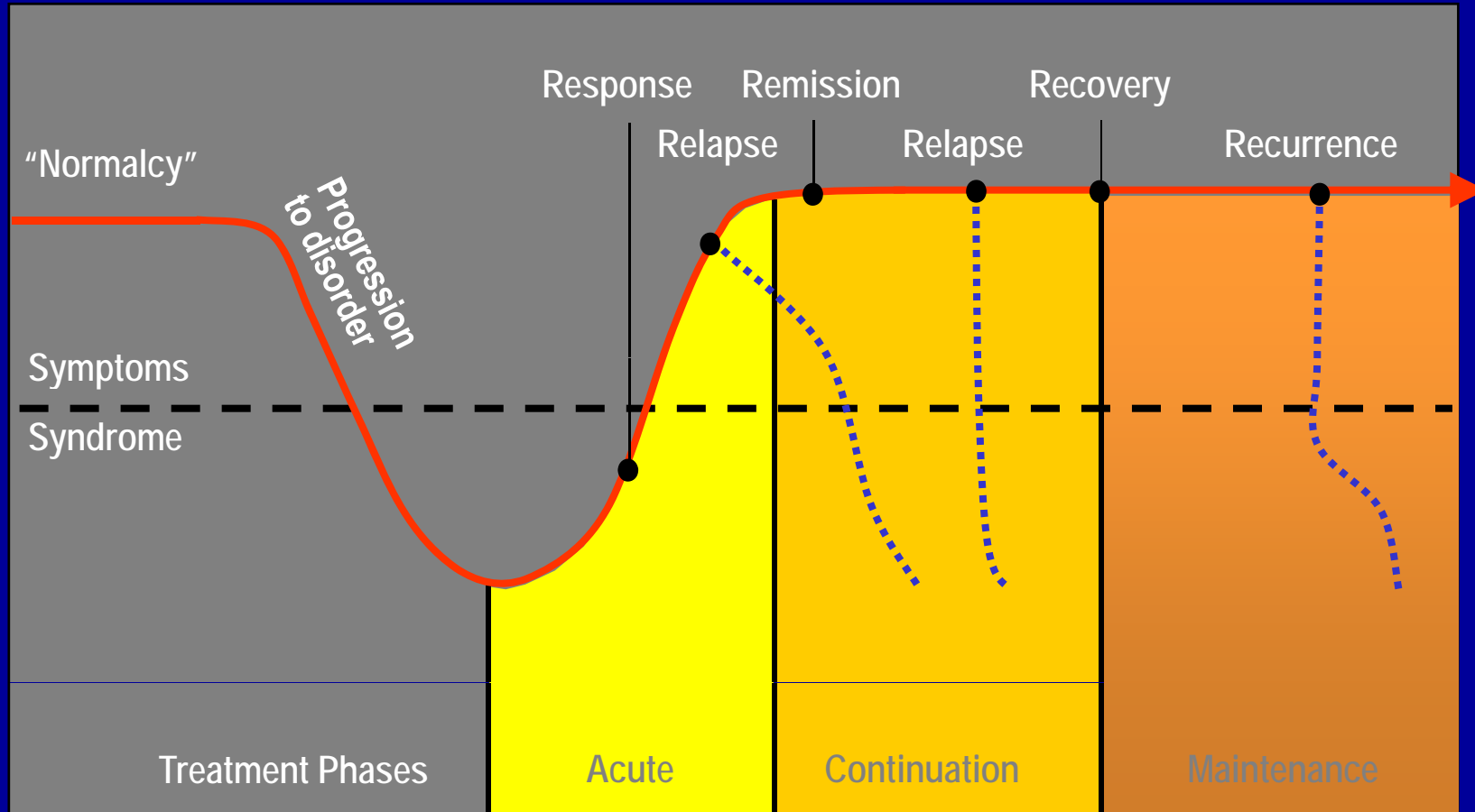
N = total number of comparative studies used in each analysis; n = combined number of patients used in each analysis; larger Hazard Ratios indicate greater risk of discontinuation on the comparator relative to olanzapine

Stauffer V, et al. Presented at the 2005 International Congress on Schizophrenia Research. Savannah, Georgia. April, 2005.

IC-SOHO study: Mean Change in Depressive CGI-S At 3, 6 and 12 Months; Adjusted for Baseline Differences with Treatment Group Comparisons

Treatment group	3 month change mean (SEM)	6 month change mean (SEM)	12 month change mean (SEM)
Olanzapine (n=3222)	-0.82 (0.04)	-1.11 (0.04)	-1.23 (0.04)
Quetiapine (n=189)	-0.40 (0.08)	-0.83 (0.09)	-0.90 (0.09)
Risperidone (n=1116)	-0.62 (0.05)	-0.91 (0.05)	-1.05 (0.05)
Haloperidol (n=256)	-0.49 (0.08)	-0.67 (0.08)	-0.86 (0.08)
Comparison	P-value for 3 month change	P-value for 6 month change	P-value for 12 month change
Olanzapine vs Quetiapine	<0.001	0.001	<0.001
Olanzapine vs Risperidone	<0.001	<0.001	<0.001
Olanzapine vs Haloperidol	<0.001	<0.001	<0.001
Quetiapine vs Haloperidol	0.413	0.148	0.763
Risperidone vs Haloperidol	0.066	0.003	0.021
Quetiapine vs Risperidone	0.008	0.376	0.100

Course/Treatment Phases of Unipolar Depression



Kupfer DJ. *J Clin Psychiatry*. 1991;52(suppl):28-34.
AHCPR. Rockville, Maryland: US Dept of Health and Human Services; 1993. Publication 93-0551.

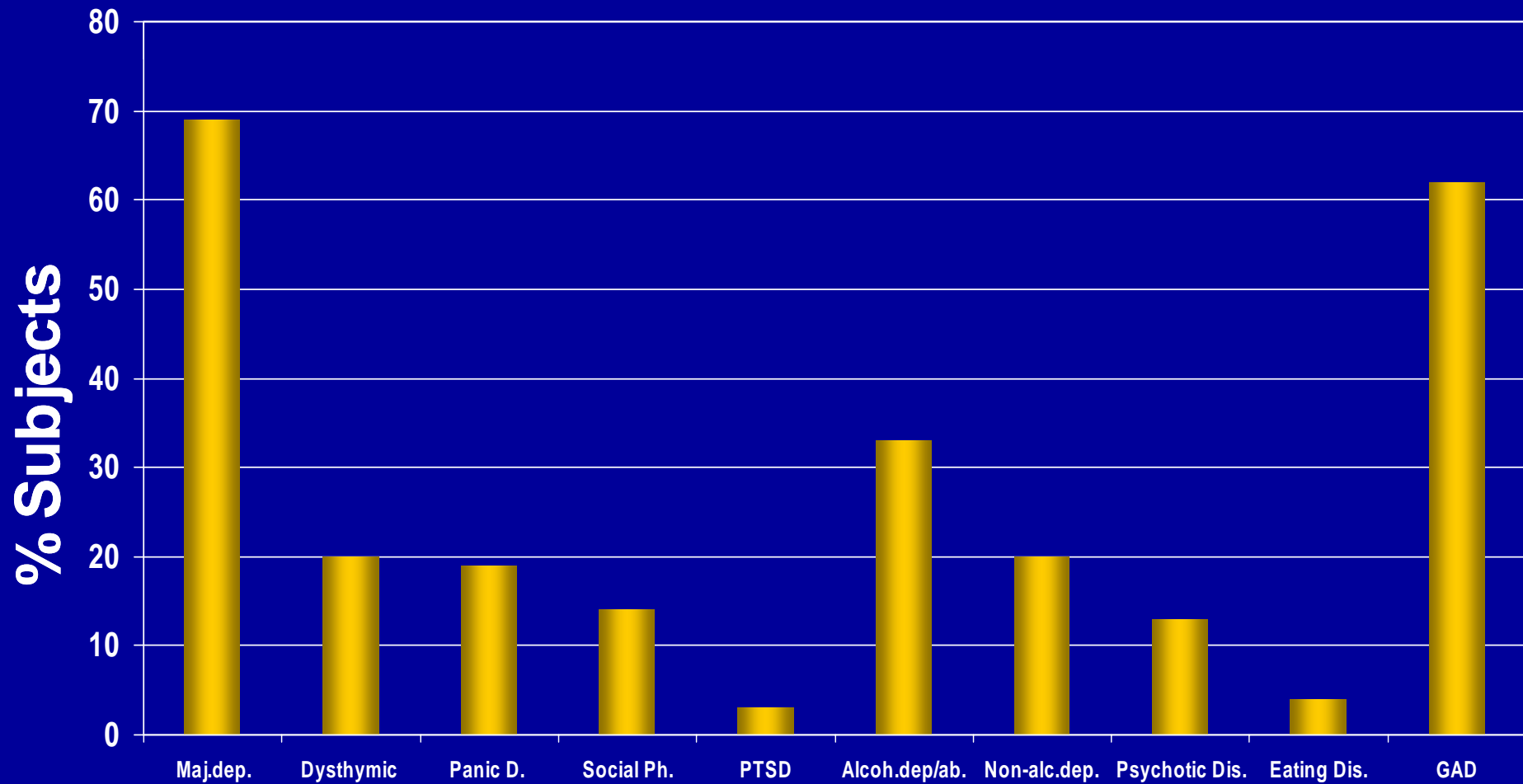
Time/Phase of Suicide and Suicide Attempts in Unipolar and Bipolar Affective Disorders

- Depression: 79-89%
- Dysphoric mania: 11-20%
- Euthymia (no symptoms): 0-1%

100 Consecutive Suicide Attempters

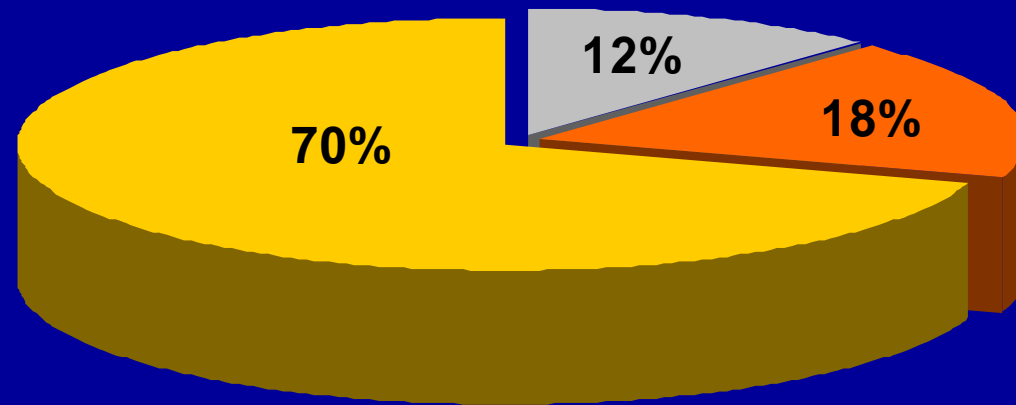
- Budapest
- Age: 18-65 years
- Suicide methods were drug overdose (96%) and poisoning with other chemicals (4%)
- They were interviewed within 24 hours after their suicide attempts

Current Threshold Disorders



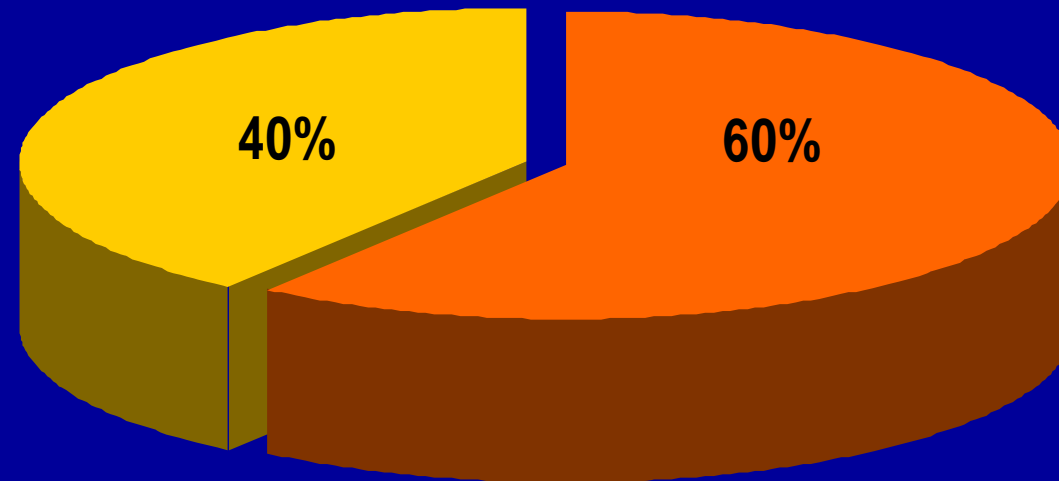
Balazs J, et al. *J Affect Disord.* 2003 Sep;76(1-3):113-9.

Comorbidity of Threshold Disorders



- 0 CURRENT MENTAL DISORDER
- 1 CURRENT MENTAL DISORDER
- 2 OR MORE CURRENT MENTAL DISORDERS

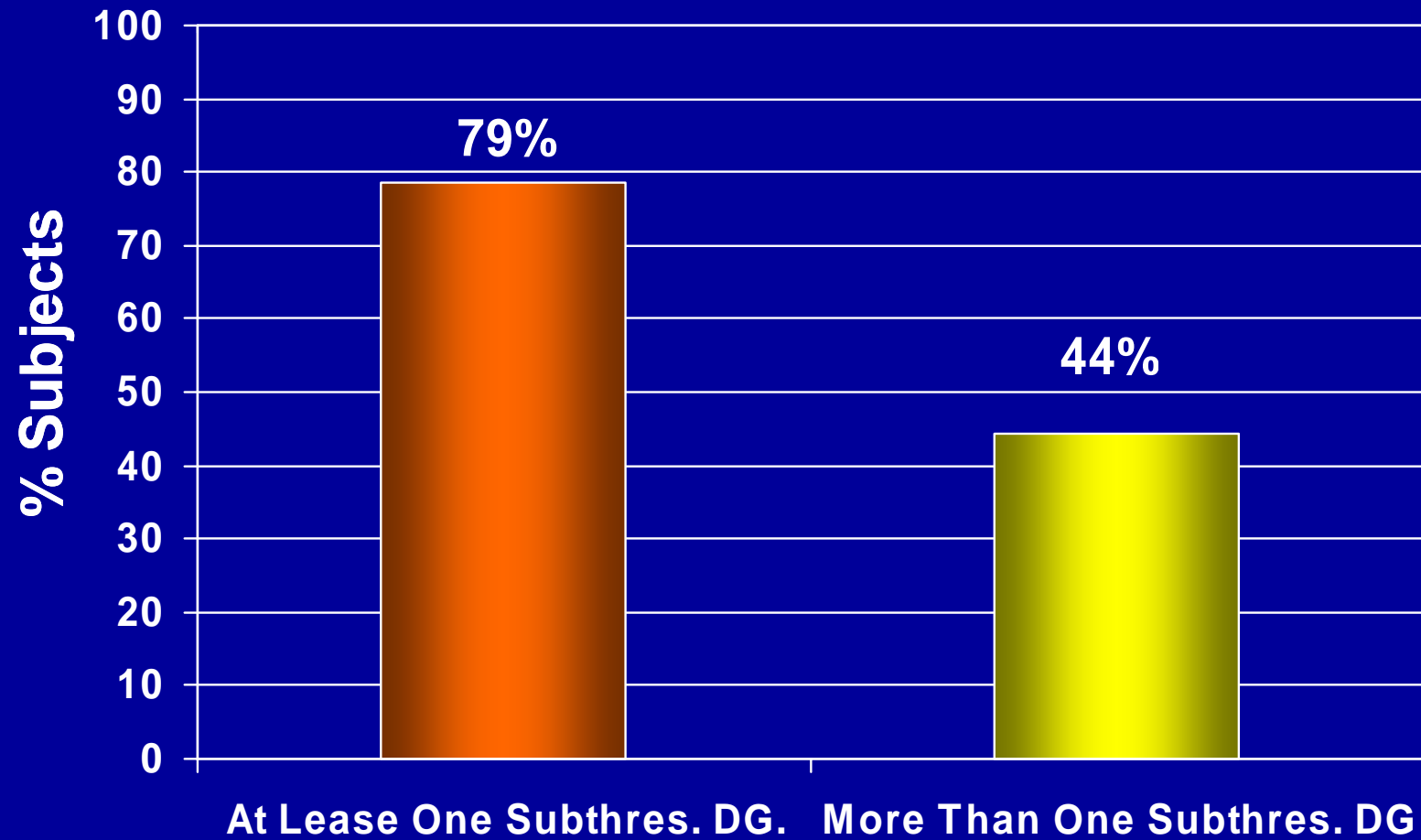
Major Depressive Episodes



■ FIRST MAJOR DEPRESSIVE EPISODE

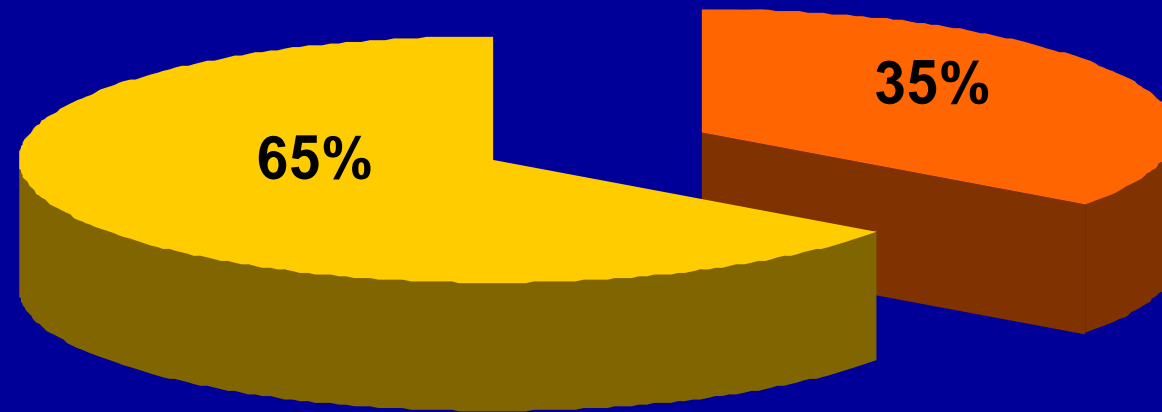
■ RECURRENT MAJOR DEPRESSIVE EPISODE

Subthreshold Forms



Balazs J, et al. *J Affect Disord.* 2003 Sep;76(1-3):113-9.

Major Depression – Current And Bipolar Disorder



■ HISTORY OF PREVIOUS HYPO/MANIC EPISODE

■ NO HISTORY OF PREVIOUS HYPO/MANIC EPISODE

Association Between Suicide and Antidepressants?

- n=48,277
- 77 fatal suicides
- Fatal suicides: absolute rates/rates corrected for treatment years: NS
 - SSRIs: 0.15%/0.58%
 - Other ADs: 0.20%/0.76%
 - Placebo: 0.10%/0.45%
 - Conclusion: No association between suicide and antidepressants

Association Between Suicide Attempts and Antidepressants?

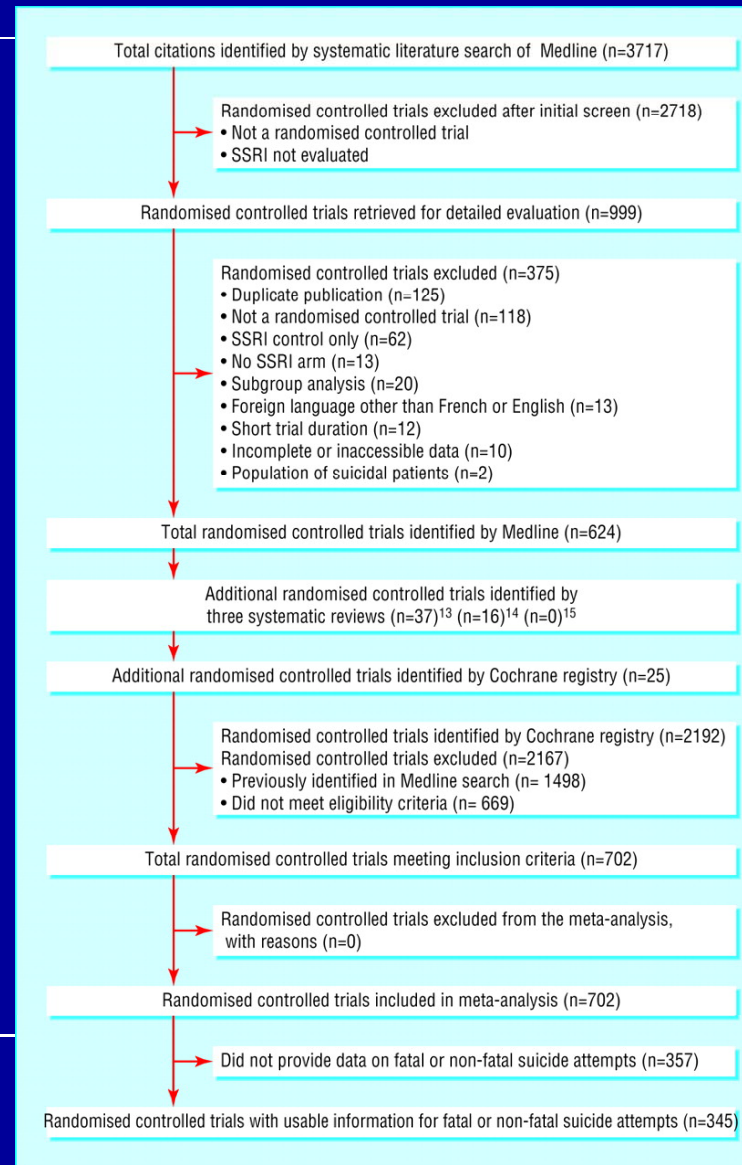
Results of a metaanalysis of SSRIs

- 702 studies included
- 87,650 patients
- “A significant increase in the odds (OR 2.28, 95% CI 1.14-4.55, number needed to harm: 684) of suicide attempts was observed for patients receiving SSRIs compared with placebo.”

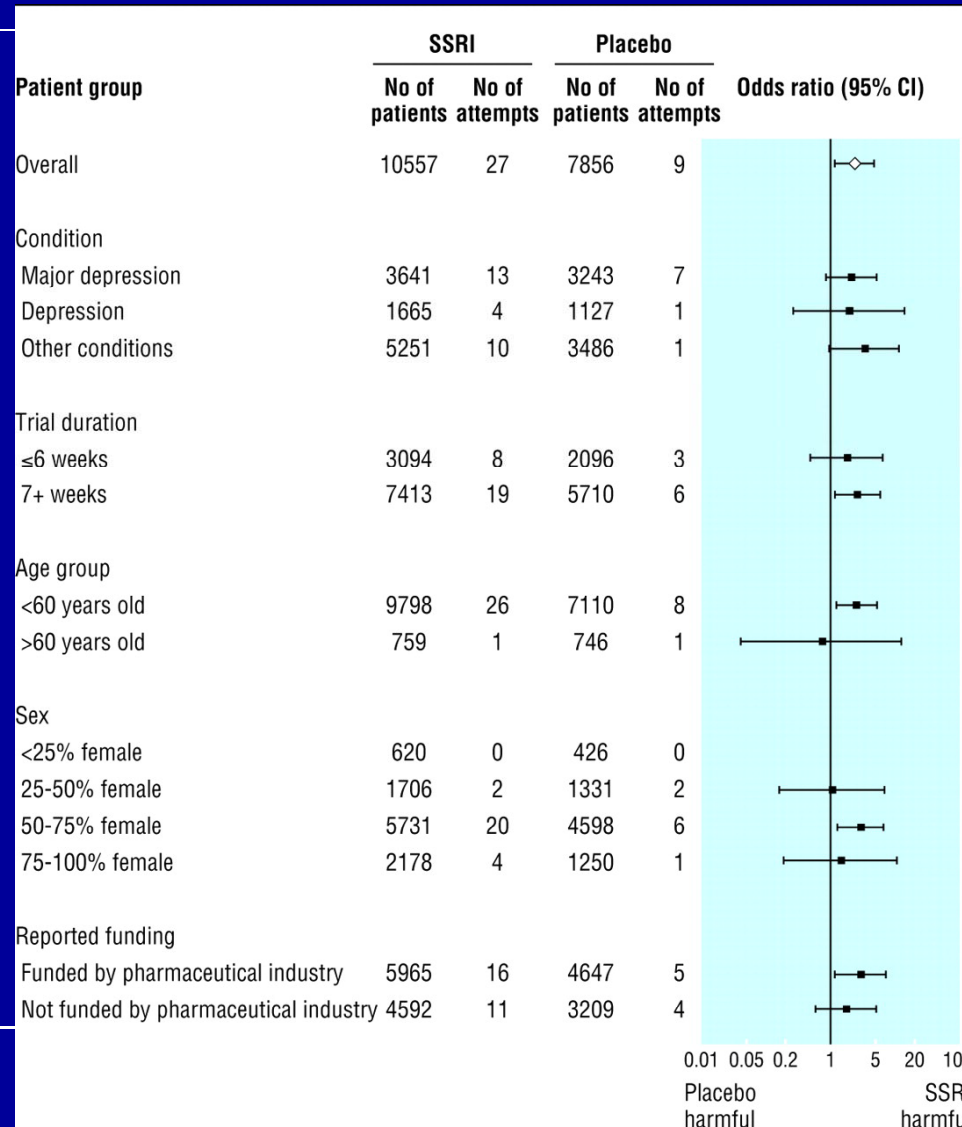
Identification and Inclusion of Trials

Usable information for fatal and nonfatal suicide attempts:

- 345 trials
- 36,445 patients
- 143 suicide attempts

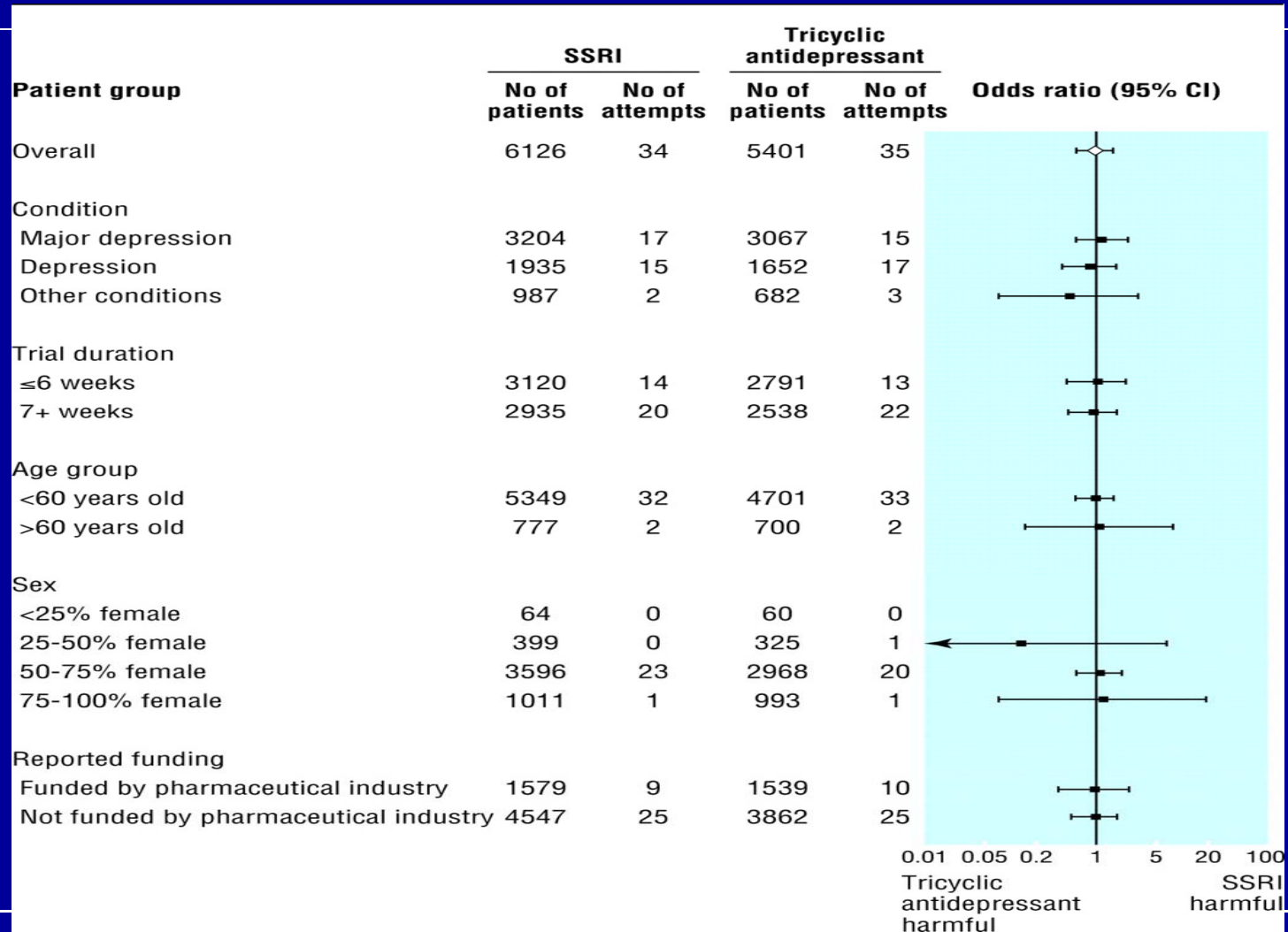


Fatal and Non-Fatal Suicide Attempts in SSRI Trials and Placebo Trials



Fergusson D, et al. *BMJ*. 2005 Feb 19;330(7488):396

Fatal and Non-Fatal Suicide Attempts in SSRI Trials and Trials Studying Tricyclic Antidepressants



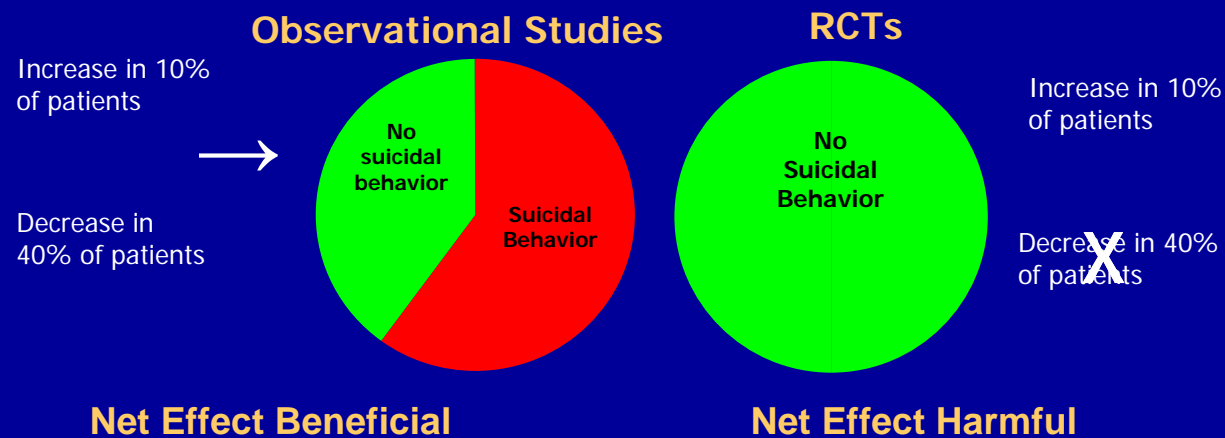
Fergusson, D. et al. *BMJ*. 2005;330:396.

Suicide Risk in Children and Adolescents

- FDA – label changes
- “We found some weak evidence of an increased risk of non-fatal self harm for current SSRI use among those aged 18 or younger”

Possible Reasons for the Antidepressant – Suicide Relationship

- Bipolar disorder misdiagnosed/underdiagnosed
 - 35-60% of first episodes are depressive in nature (children and adolescents!)
 - 30% of patients with depression or anxiety may have bipolar disorder
- Patients with suicide risk are excluded from randomized clinical trials (RCTs)
 - only increases are possible to detect - because patients whose suicidal ideation/behaviour may decrease are excluded



Manning JS, et al. *Compr Psychiatry*. 1997;38(2):102-8.; And presented at: The National Depressive and Manic-Depressive Association, 2001.

The Relationship Between Antidepressant Prescription Rates and Rate of Early Adolescent Suicide

Robert D. Gibbons, Ph.D.

Kwan Hur, Ph.D.

Dulal K. Bhaumik, Ph.D.

J. John Mann, M.D.

Objective: In 2002, 264 children and adolescents ages 5–14 died by suicide in the United States, the fifth leading cause of death. Of these suicides, 260 were in the 10–14 year age group, making suicide the third largest cause of death behind accidents and malignancy. Although 60% of suicides in the general population occur in the midst of a mood disorder, usually untreated, little is known about the relationship between treatment of mood dis-

associations at the county level across the United States.

Method: National county-level suicide rate data among children ages 5–14 were broken down by sex, income, and race during the period 1996–1998. National county-level antidepressant prescription rate data were expressed as number of pills prescribed per person. The primary outcome measure was the suicide rate in each county expressed as number of suicides for a given population size.

Results: After adjustment for sex, race, income, access to mental health care, and county-to-county variability in suicide rates, higher SSRI prescription rates were associated with lower suicide rates in children and adolescents.

Conclusions: The aggregate nature of these observational data precludes a direct causal interpretation of the results. More SSRI prescriptions are associated with lower suicide rates in children and may reflect antidepressant efficacy, treatment compliance, better quality mental health care, and low toxicity in the event of a suicide attempt by overdose.

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study examined the association between antidepressant medication prescription rate and suicide rate in children ages 5–14 prior to the FDA findings by analyzing

(Am J Psychiatry 2006; 163:1898–1904)

Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents

Robert D. Gibbons, Ph.D.

C. Hendricks Brown, Ph.D.

Kwan Hur, Ph.D.

Sue M. Marcus, Ph.D.

Dulal K. Bhaumik, Ph.D.

Joëlle A. Erkens, Pharm.D., Ph.D.

Ron M.C. Herings, Pharm.D., Ph.D.

J. John Mann, M.D.

Objective: In 2003 and 2004, U.S. and European regulators issued public health warnings about a possible association between antidepressants and suicidal thinking and behavior. The authors assessed whether these warnings discouraged use of antidepressants in children and adolescents and whether they led to increases in suicide rates as a result of untreated depression.

Method: The authors examined U.S. and Dutch data on prescription rates for selective serotonin reuptake inhibitors (SSRIs) from 2003 to 2005 in children and adolescents (patients up to age 19), as well as suicide rates for children and adolescents, using available data (through 2004 in the United States and through 2005 in the Netherlands). They used Poisson regression analyses to determine the overall association between antidepressant prescription rates and suicide rates, adjusted for sex and age, during the periods preceding and immediately following the public health warnings.

Results: SSRI prescriptions for youths decreased by approximately 22% in both the United States and the Netherlands after the warnings were issued. In the Netherlands, the youth suicide rate increased by 49% between 2003 and 2005 and shows a significant inverse association with SSRI prescriptions. In the United States, youth suicide rates increased by 14% between 2003 and 2004, which is the largest year-to-year change in suicide rates in this population since the Centers for Disease Control and Prevention began systematically collecting suicide data in 1979.

Conclusions: In both the United States and the Netherlands, SSRI prescriptions for children and adolescents decreased after U.S. and European regulatory agencies issued warnings about a possible suicide risk with antidepressant use in pediatric patients, and these decreases were associated with increases in suicide rates in children and adolescents.

(Am J Psychiatry 2007; 164:1356–1363)

FIGURE 1. SSRI Prescription Rates in the United States, 2002–2005, Stratified by Age Group and Expressed as a Percentage of the 2003 Rate

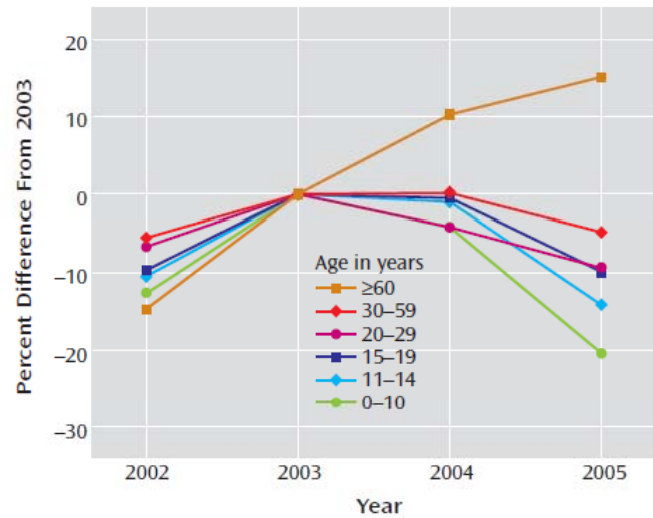


FIGURE 2. Suicide Rate in Children and Adolescents (Ages 5–19 Years) in the United States, 1988–2004

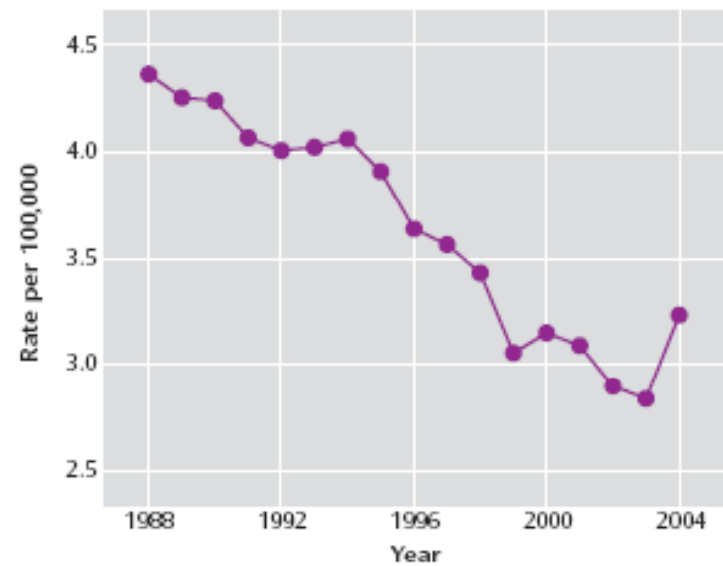


FIGURE 3. Suicide Rate in Older Adults (Age 60 Years and Over) in the United States, 1988–2004

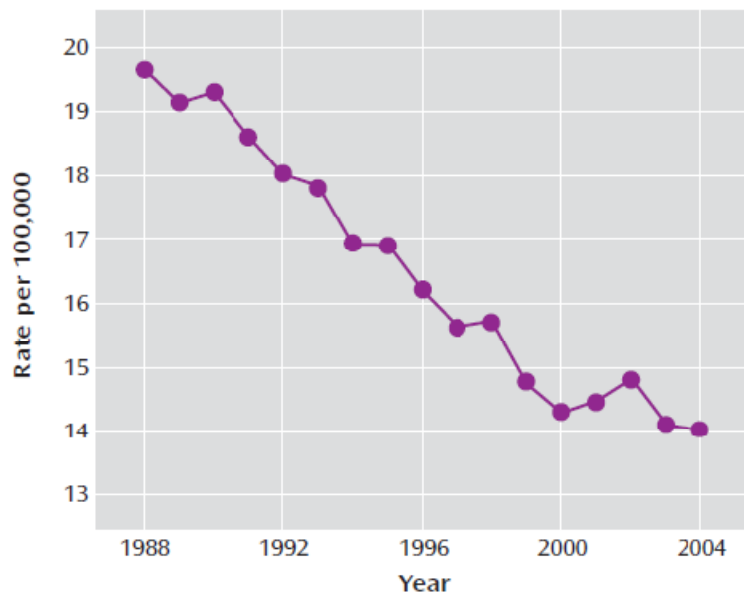
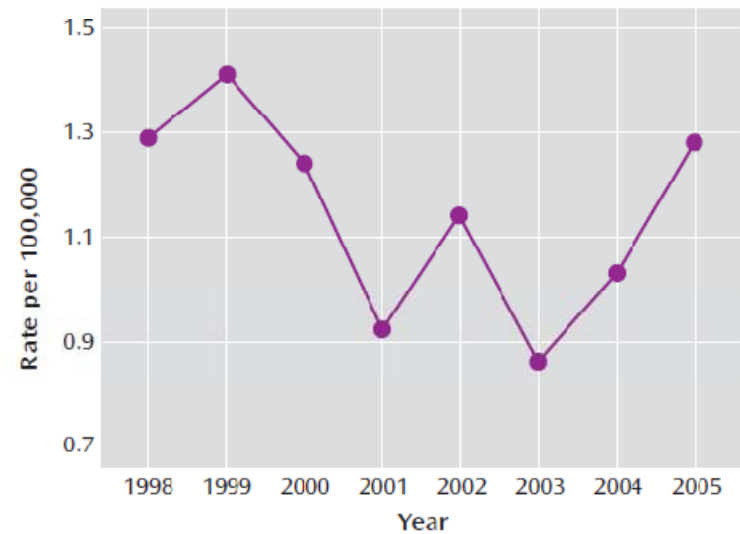
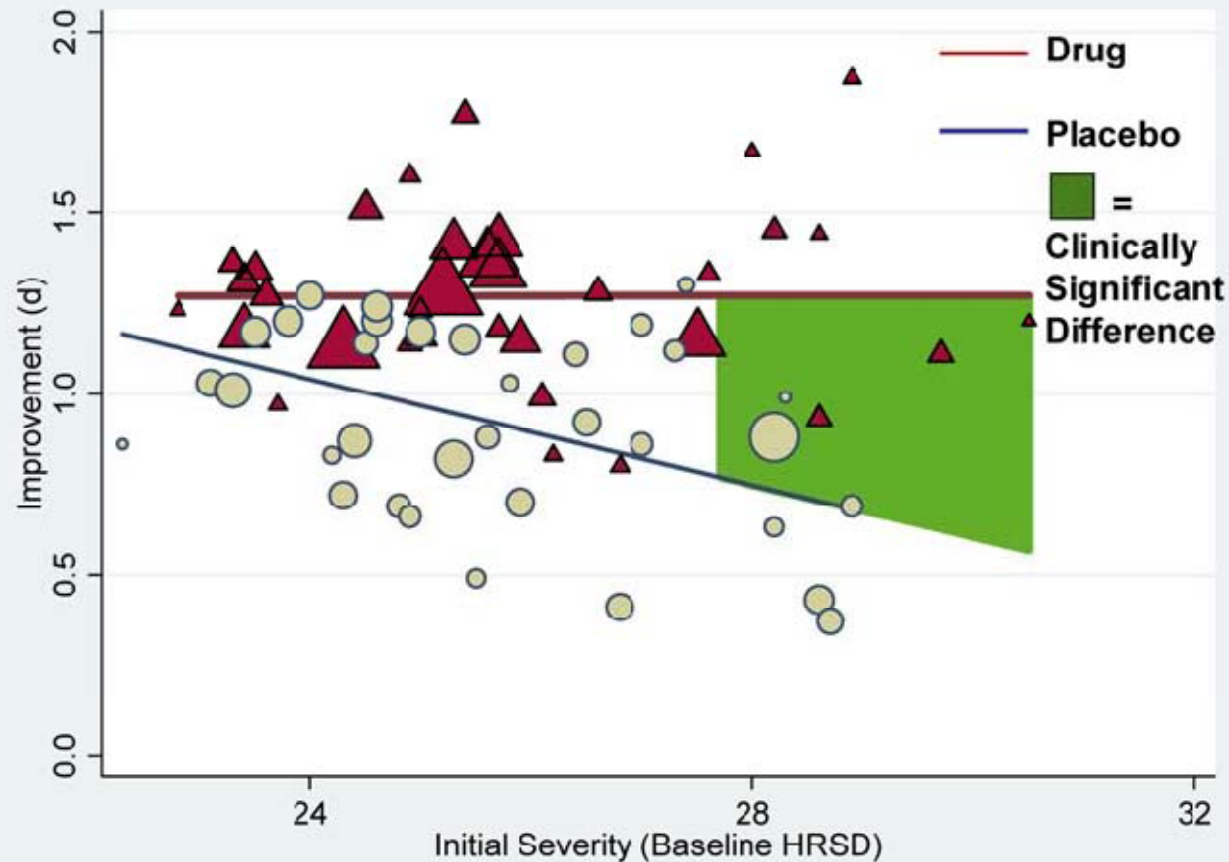


FIGURE 5. Suicide Rate in Children and Adolescents (Up to Age 19) in the Netherlands, 1998–2005





OPEN ACCESS Freely available online

PLOS MEDICINE

Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration

Irving Kirsch^{1*}, Brett J. Deacon², Tania B. Huedo-Medina³, Alan Scoboria⁴, Thomas J. Moore⁵, Blair T. Johnson³

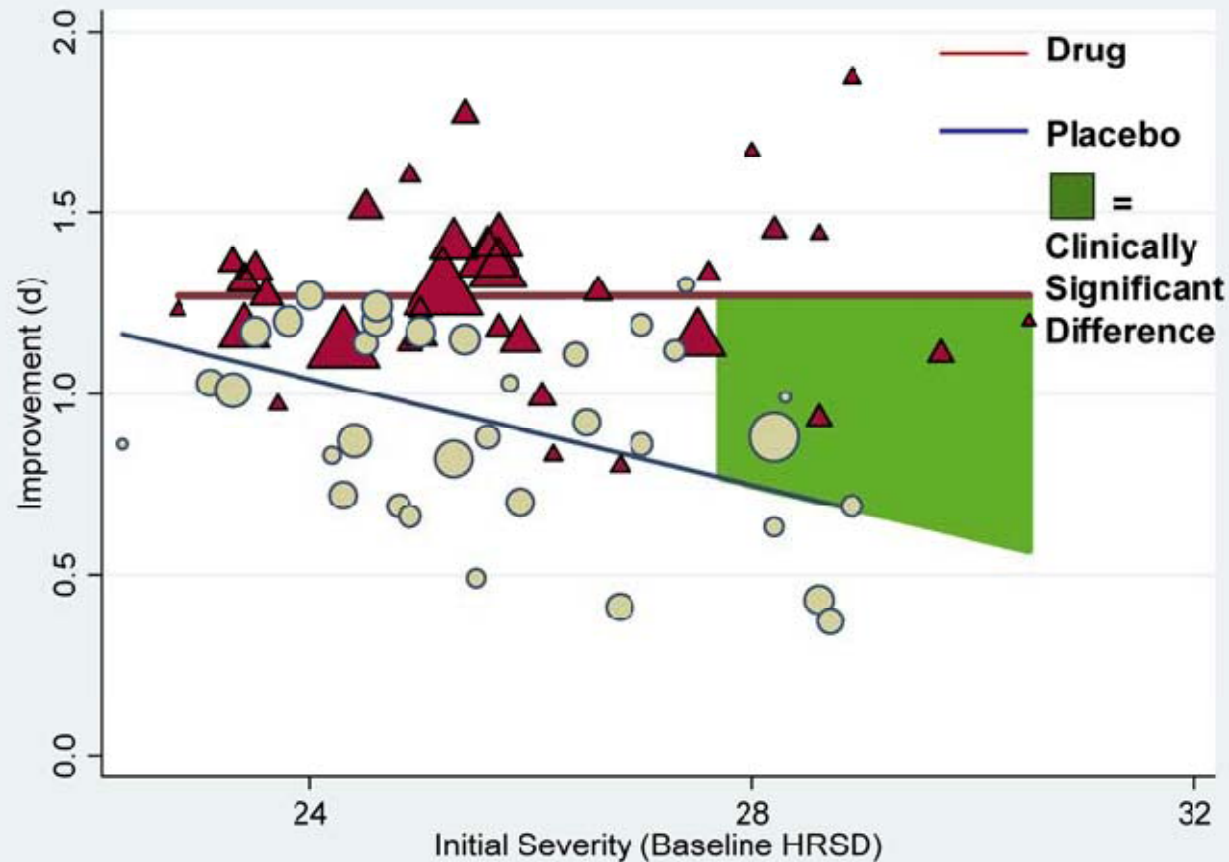


Figure 3. Mean Standardized Improvement as a Function of Initial Severity and Treatment Group, Including Only Trials Whose Samples Had High Initial Severity

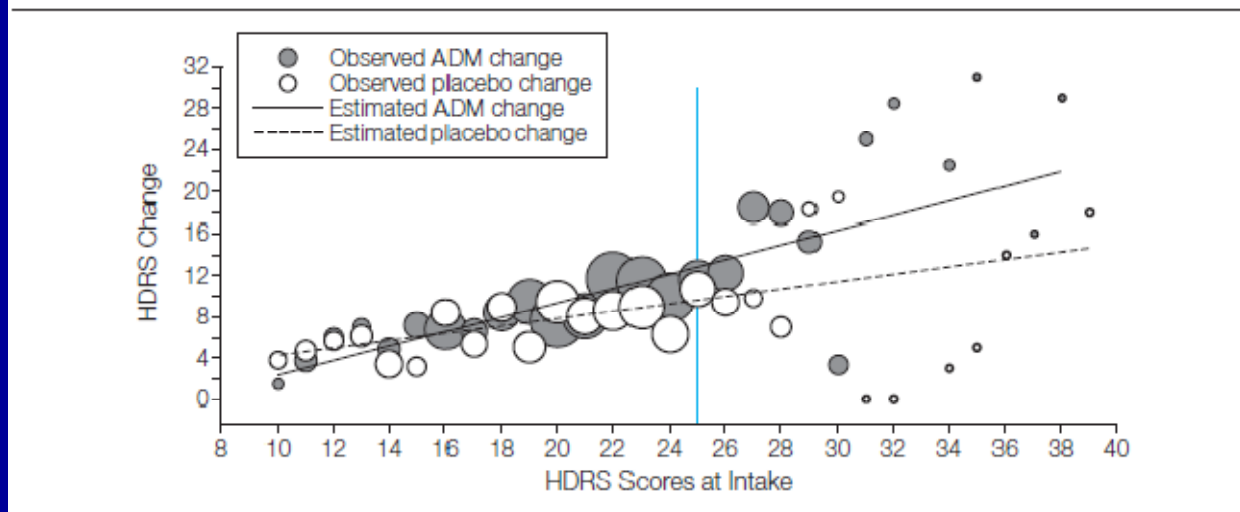
Drug improvement is portrayed as red triangles around their solid red regression line and placebo improvement as blue circles around their dashed blue regression line; the green shaded area indicates the point at which comparisons of drug versus placebo reach the NICE clinical significance criterion of $d = 0.50$. Plotted values are sized according to their weight in analyses.

doi:10.1371/journal.pmed.0050045.g003

Antidepressant Drug Effects and Depression Severity

A Patient-Level Meta-analysis

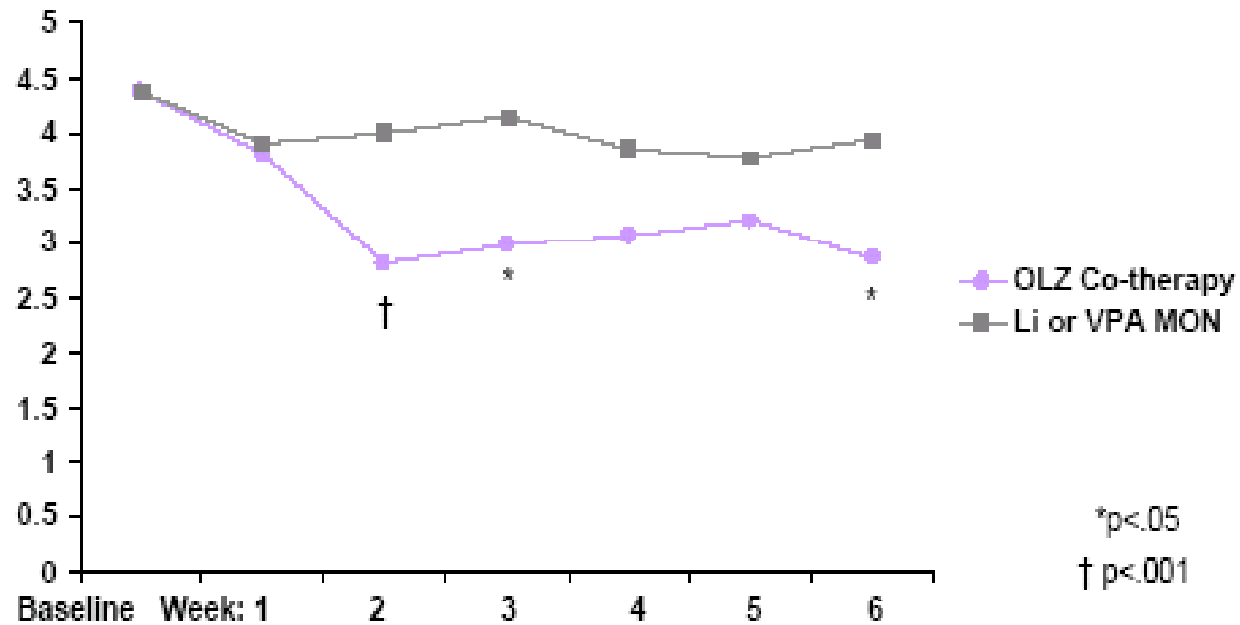
Figure 2. Observed and Estimated Change in HDRS Scores Following Treatment With ADM and Placebo



Circles represent observed (raw) mean change in depressive symptoms from intake to the end of treatment at each initial Hamilton Depression Rating Scale (HDRS) score for both the antidepressant medication (ADM) and placebo conditions. The size (area) of the circles is proportional to the number of data points that contributed to each mean. Regression lines represent estimates of change in depression symptoms from intake to end of treatment for ADM and placebo conditions as a function of baseline symptom severity. These regression lines were estimated from a model of the baseline severity \times treatment interaction, controlling for the effects of the study from which the data originated. The National Institute for Clinical Excellence threshold for clinical significance (an HDRS point difference ≥ 3) was met for intake HDRS scores of 25 or greater, indicated by the blue line.

OLZ Co-Therapy Improves Suicidality Factors in Mixed Mania Patients

OLANZAPINE CO-THERAPY WITH EITHER LITHIUM OR VALPROATE SUICIDALITY FACTOR 4: DYSPHORIA

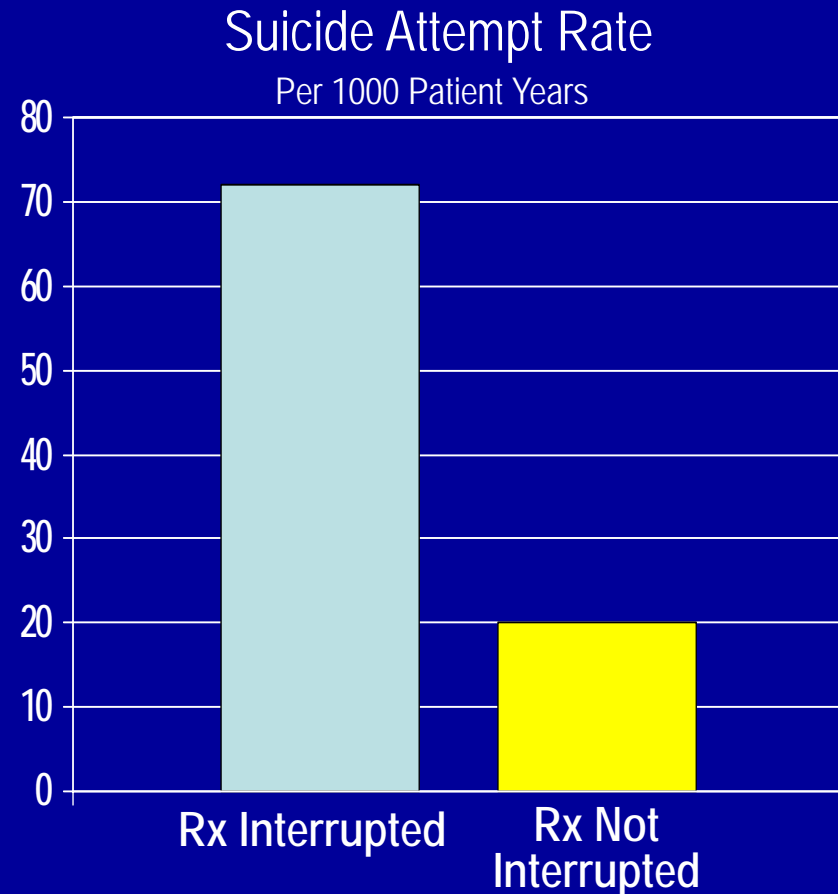


OLZ Co-therapy	n=36	34	33	31	28	29
Li or VPA MON	n=22	20	19	16	14	13

Houston JP, et al. OLZ Co-Therapy Improves Suicidality Factors in Mixed Mania Patients. Abstract presented at the American Psychological Association, May, 2004. New York, NY

Anti-Psychotic Medication Compliance and Suicide Risk

- 603 schizophrenia patients, aged 15-45 yrs
- Prescribed olanzapine or risperidone
- 33% interrupted treatment for ≥ 30 days
- Suicide attempt rate
 - 20.0/1000 person years (uninterrupted)
 - 72.1/1000 person years (interrupted)
 - A 4-fold increased risk for attempting suicide among patients with drug holidays
- Patients who do not refill prescriptions can be identified in the pharmacy and are most likely those with an increased risk to commit suicide



Suicidal Ideation: Olanzapine vs Haloperidol Treatment

- Comparison of suicidal ideation in patients with schizophrenia, schizoaffective and schizophreniform disorders treated with olanzapine or haloperidol
- Post hoc analysis of data from a subset of patients with baseline scores for suicidal ideation >0 as measured by MADRS-10
- Changes from baseline to last acute observation in MADRS-10 scores and associated suicidal ideation factors were evaluated, testing for differences between treatment groups
- Results: After 6 weeks of treatment, significantly lower MADRS-10 scores were observed in the olanzapine-treated patients as compared to the haloperidol-treated patients

Suicidality: Monotherapy vs Olanzapine Co-Therapy

- 6-week, double-blind, placebo-controlled study on olanzapine (OLZ) combined with either lithium (Li) or valproate (VPA) vs Li or VPA monotherapy in mixed bipolar episodes in partially non-responsive patients
- A post-hoc analysis of a subset of patients (n=58) with non-zero baseline suicidality scores to assess the impact of treatment on 5 factors associated with suicidality:
 - Restlessness, psychosis, somatization, psychological depression, agitation
- Results:
 - Significant suicidality (HAM-D-3) reduction occurred by Week 1 in patients treated with OLZ co-therapy (-.84; n=36) vs. MON (-.42; n=21; $P=.042$)
 - OLZ co-therapy-treated patients showed greater improvement ($P<.05$) in somatization by Week 1; restlessness, psychological depression, and agitation by Week 2; and psychosis by Week 3. The early statistically significant difference in restlessness became non-significant after Week 3 for OLZ co-therapy vs MON

Protective Effect of SGAs on Suicide

- Retrospective, case-controlled evaluation over a 5-year period
- 756 patients (4486 admissions)
- 56.6% male, Mean age 39.1 +/- 13.5 years
- Of 378 patients who attempted suicide (index group)
 - 16.1% were taking an SGA (risperidone, olanzapine, or clozapine)
 - 37.0% did not receive an SGA

(P =0.0001; Odds Ratio = 3.54 SGA protective)

Conclusions

- Depression (depressive syndromes including “subthreshold” depression) is a major risk factor for suicide and suicide attempts
- Second generation antipsychotics are more effective in the treatment of depression in schizophrenia than first generation antipsychotics and they are related to lower rates of suicidal behavior
- Comorbidity increases the risk of suicide and suicide attempts
- The benefits of antidepressants far outweigh their possible risks, however better diagnosis (bipolar disorders!) and close monitoring could decrease the risk