

ISCTM Symposium/Chicago, 2006

***Long-Term Treatment
for Bipolar Disorders:
Overview***

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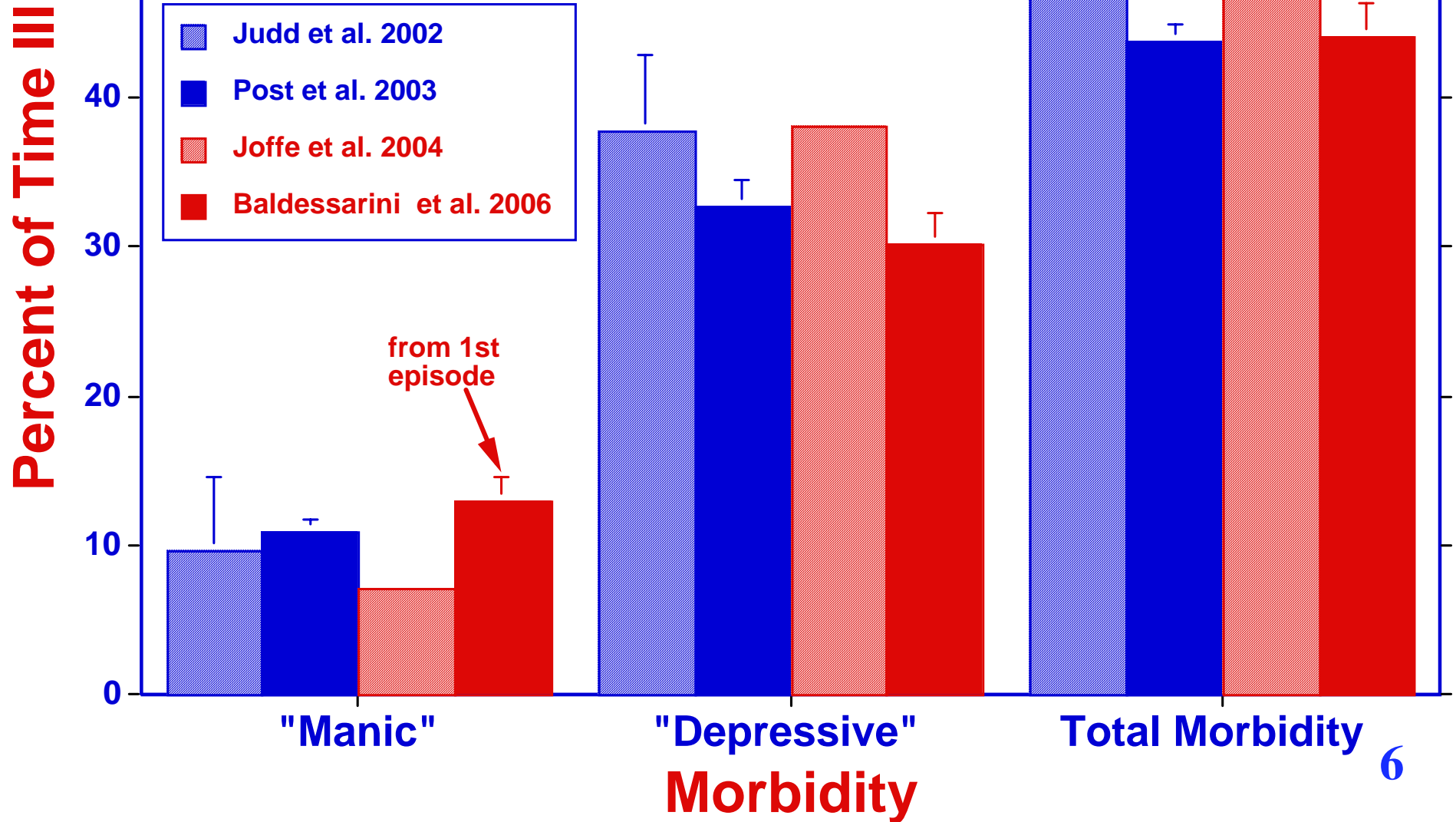
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Current US treatments for bipolar disorders (2006)

Agents	<i>Major Mania</i>	<i>Depression</i>	<i>Mixed States</i>	<i>Long-term Maintenance</i>	<i>BP-II or Cyclothymia</i>	<i>Suicide</i>
Anti depressants	No	No	No	No	No	No
Lithium	Yes	No	No	Yes	No	Pending
Chlorpromazine	Yes	No	No	No	No	No
Carbamazepine-ER	Yes	No	Yes	No	No	No
Divalproex	Yes	No	No	No	No	No
Lamotrigine	No	No	No	Yes	No	No
Oxcarbazepine	No	No	No	No	No	No
Aripiprazole	Yes	No	Yes	Yes	No	No
Olanzapine	Yes	No	Yes	Yes	No	No
ONZ+FLX	No	Yes	No	No	No	No
Quetiapine	Yes	No	No	No	No	No
Risperidone	Yes	No	No	No	No	No
RSP-depot	No	No	No	No	No	No
Ziprasidone	Yes	No	No	No	No	No

ER = extended release, *FLX* = fluoxetine; *ONZ* = olanzapine; *RSP* = risperidone (*depot* = IM carbohydrate microspheres). Other BPD conditions needing study: a. dysthymia, b. comorbid substance use, c. comorbid anxiety disorders, d. rapid-cycling, e. functional disability, f. all-cause mortality.

Residual Morbidity in Treated BP-I Patients

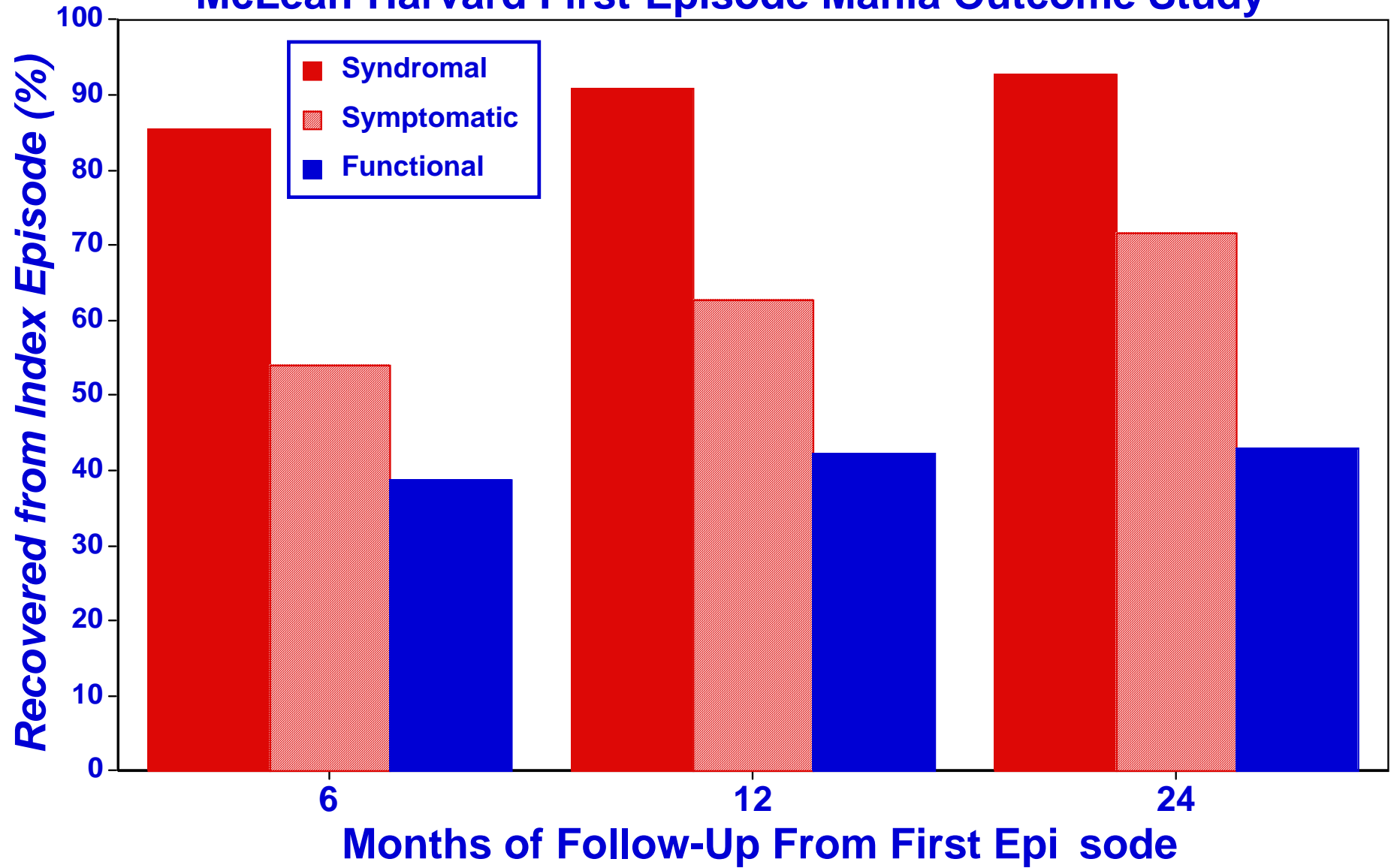


Suicidal Risk in Selected Disorders

Disorder	SMR	%/Year	%Total
Bipolar disorder	21	0.31	15.5
Severe Maj Dep r	19	0.29	14.6
Mixed drug abuse	19	0.28	14.7
Dy sthymia	11	0.17	8.6
OCD	11	0.14	8.2
Panic disorder	11	0.16	7.2
Schizophrenia	8.0	0.12	6.0
Personality Dx s	6.7	0.10	5.1
Alcohol abuse	5.3	0.08	4.2
Cancer	2.0	0.03	1.3
<i>Genl pop ulation</i>	1.00	0.015	0.72

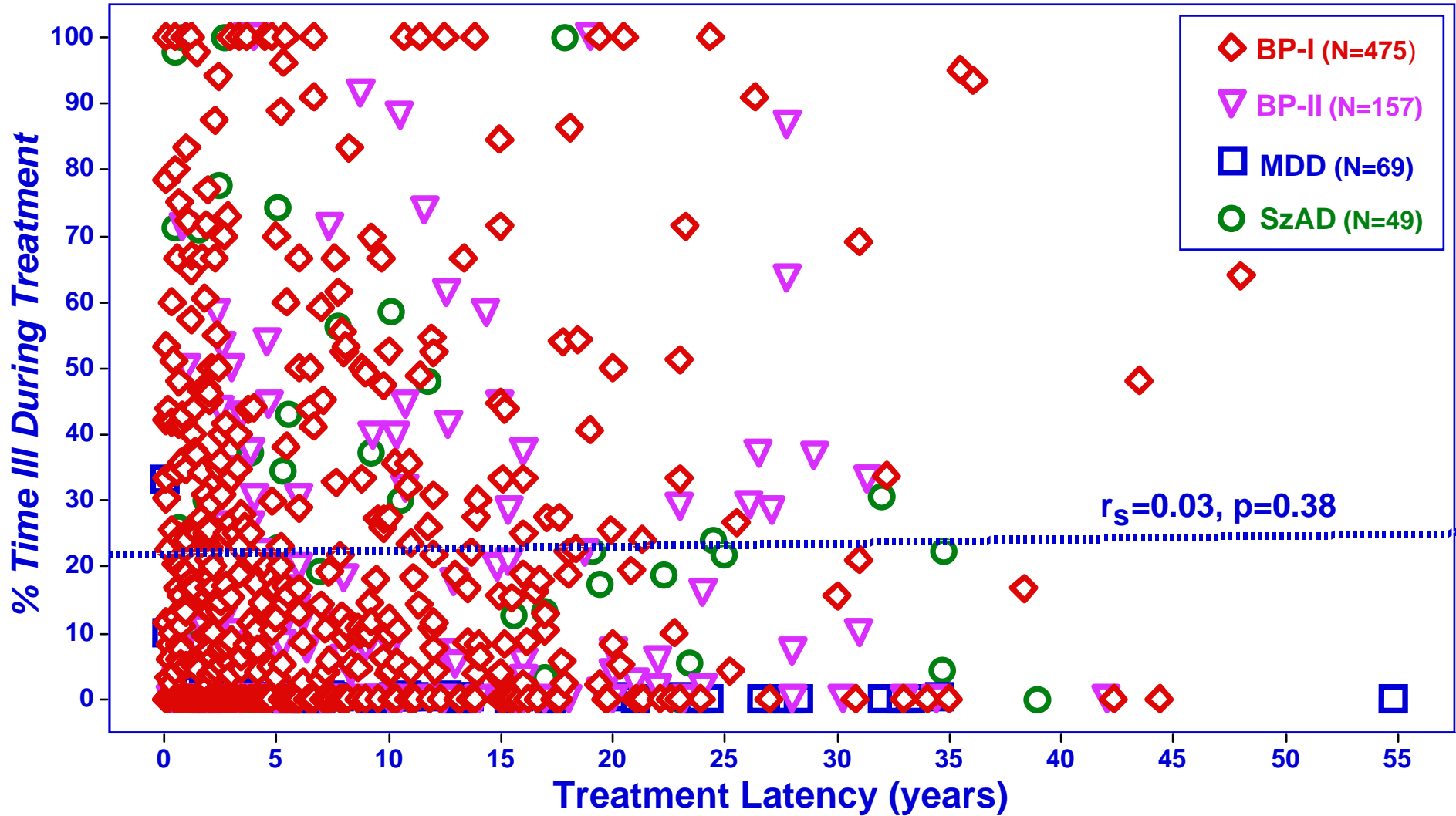
Adapted from Harris & Barraclough. Br J Psychiatry. 1997;170:205-208;
Tondo et al. CNS Drugs. 2003; 17: 491-511.

McLean-Harvard First-Episode Mania Outcome Study

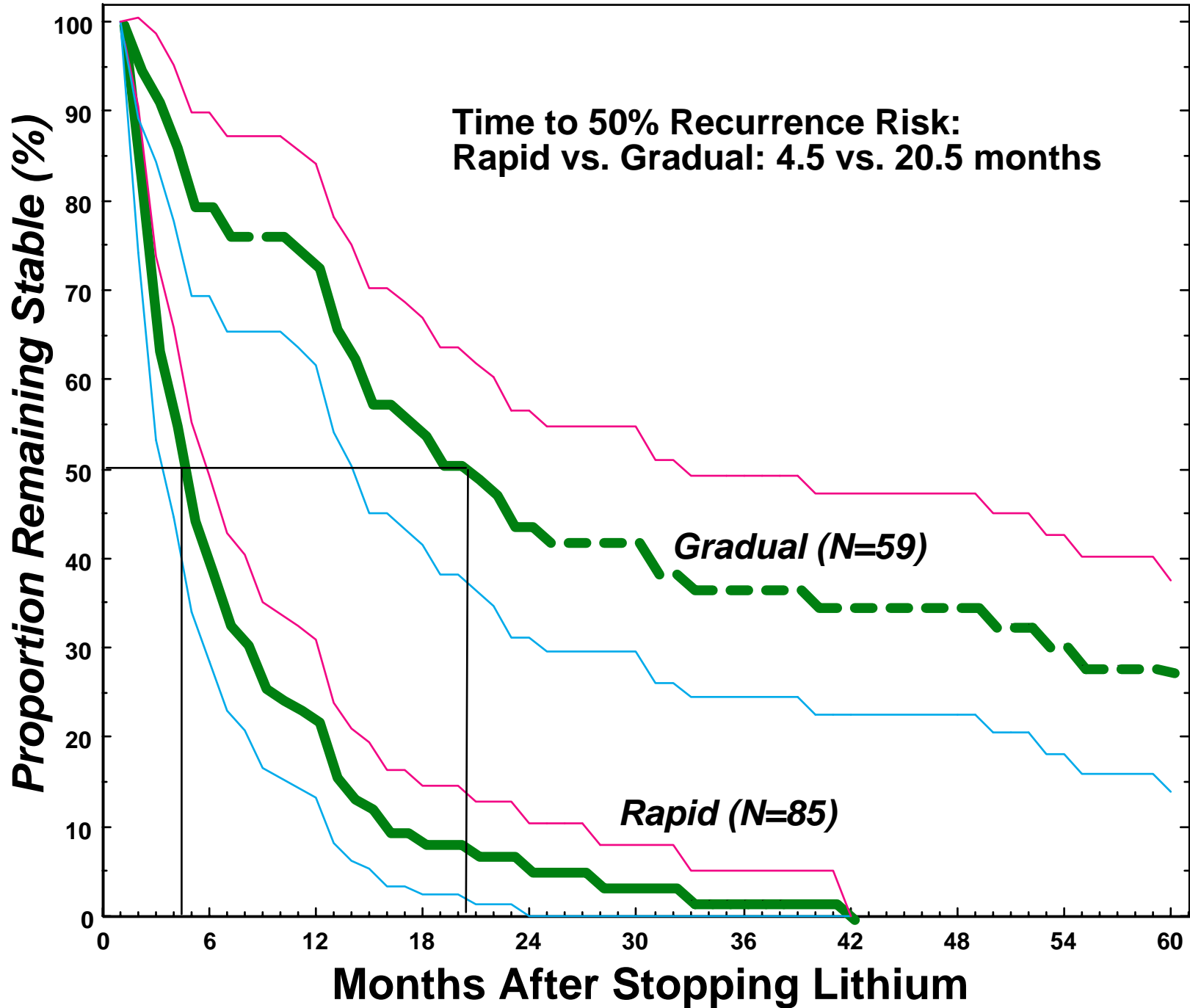


[From Tohen et al. Am J Psychiatry 2003]

Morbidity During Prophylaxis in 750 Manic-Depressives

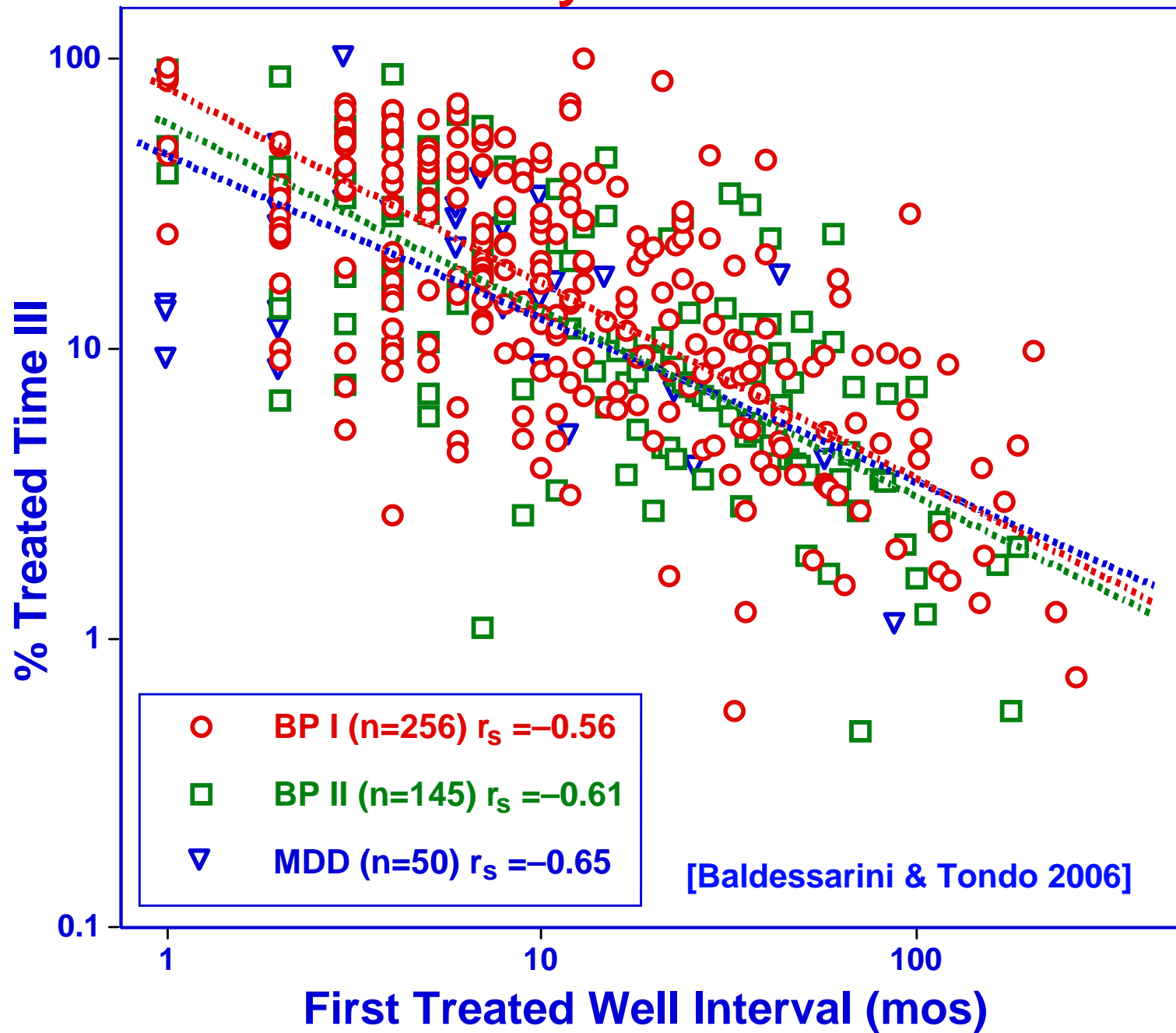


[Baethge, Baldessarini & Tondo: Can J Psychiatry 2003]



[From Baldessarini et al. J Clin Psychiatry 57: 441-448, 1996]

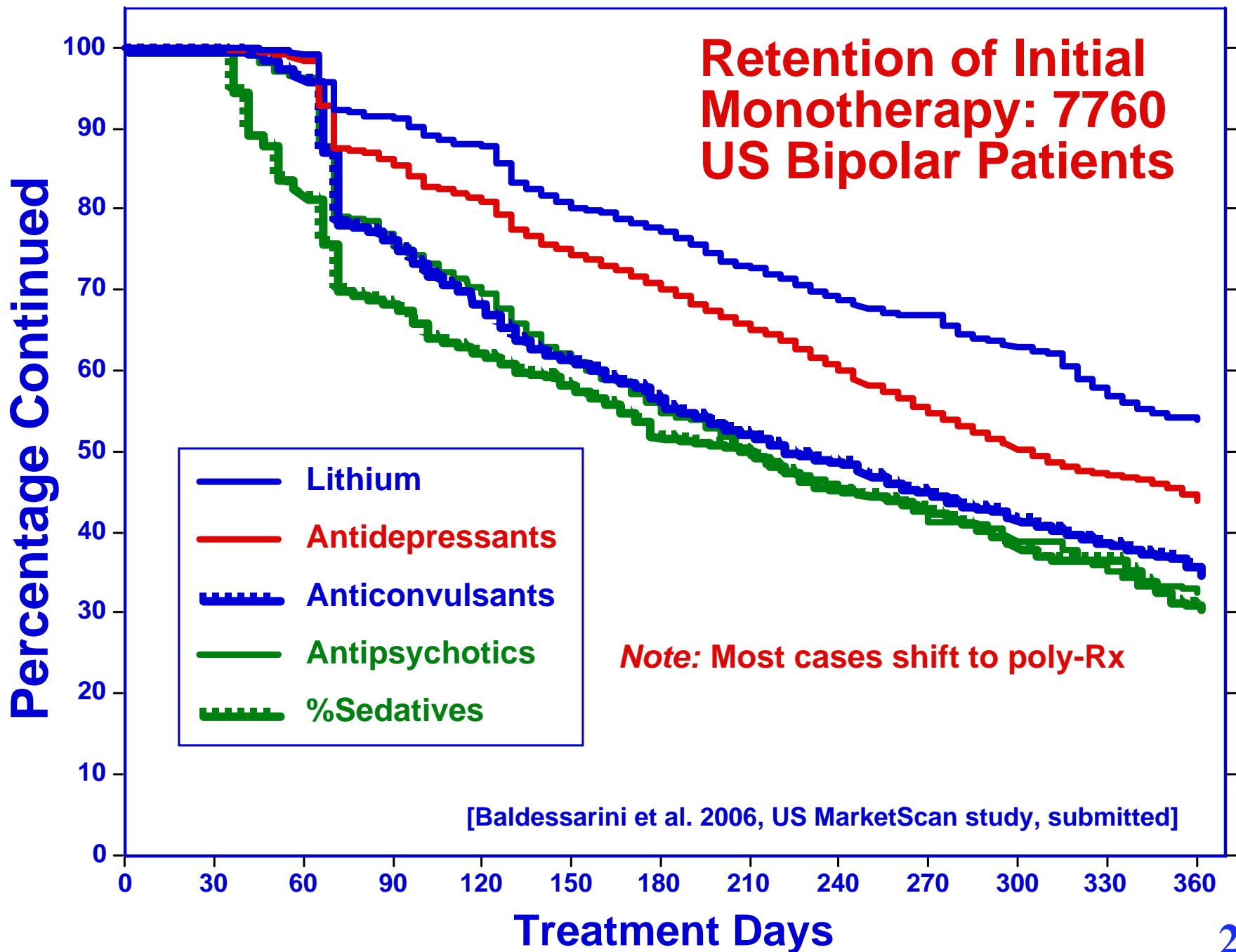
Treated Morbidity vs. First Well Interval



Long-term treatments received by 254 bipolar-I patients (1996–2002)

Agent	% of Cases	Wks of Rx
<i>Mood-stabilizers</i>	97.0	37.4
Lithium	64.0	42.8
Valproate	52.3	37.8
Carbamazepine	26.4	39.8
Gabapentin	26.4	28.1
Topiramate	11.2	24.0
Lamotrigine	10.9	24.9
<i>Antidepressants</i>	52.7	23.5
<i>Antipsychotics</i>	32.9	21.3
Typical	20.9	23.7
Atypical	16.7	18.1
<i>Benzodiazepines</i>	48.8	14.5

From Post et al: J Clin Psychiatry 2003; 64: 680–690.



Lithium: Long-term randomized controlled trials

Study	Dx	Stable (mo)	Taper (wk)	Treated (mo)	<i>Relapse Risk</i> Lithium	<i>Pbo</i>
Prien et al. 1973	BP I	?	?	24	43/101	84/104
Kane et al. 1982	BP II	?	?	24	2/10	8/12
Bowden et al. 2000*	BP I (M)	3	2	12	28/91	36/94
Bowden et al. 2002*	BP I (D)	3	2	12	56/121	66/121
Bowden et al. 2003*	BP I (Mm)	2–3	3	12	18/46	49/70
Totals					147/369	243/401
RR [95%CI]					1.52 [1.19–2.00]	

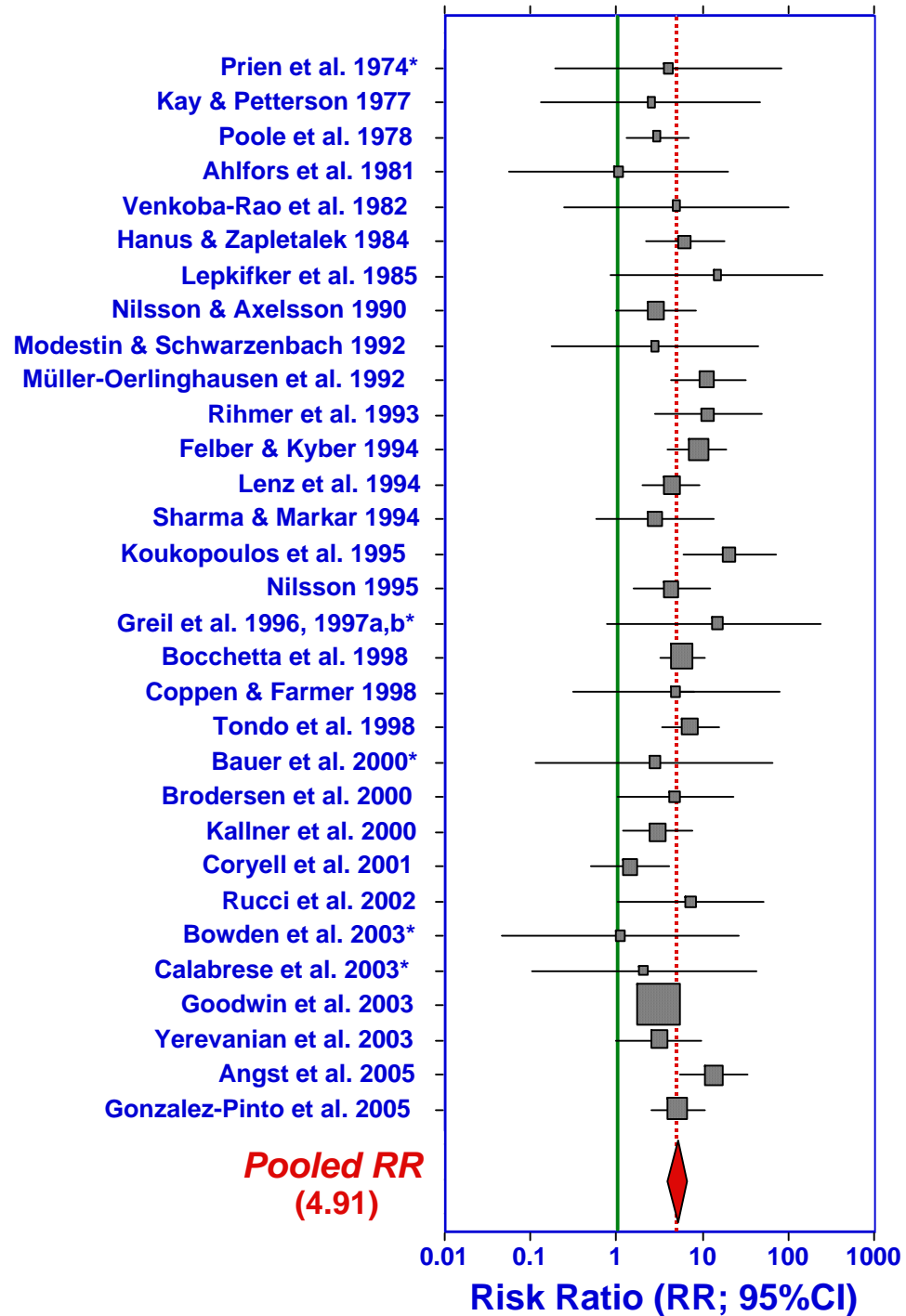
Adapted from Geddes et al. Am J Psychiatry 2004; 161: 217–222. [*] Primarily LTG trial.

Outcomes vs. new manias: Li: 37/268 (13.8%) vs. PBO: 70/297 (23.6%); RR = 1.71 [CI: 1.05–2.50].

Outcomes vs. new depressions: Li: 67/268 (25.0%) vs. PBO: 88/297 (29.6%); RR = 1.18 [CI: 0.91–1.56].

Meta-Analysis: Lithium vs. Suicides & Attempts

[Baldessarini et al. 2006]



Meta-analyses: Lithium treatment vs. suicidal risk

Conditions	Studies (N)	Risk Ratio (RR)	[95% CI]	p
All studies	34	4.91	[3.86–6.23]	<0.001
Suicides	25	4.89	[3.46–6.91]	<0.001
Attempts	20	4.86	[3.58–6.59]	<0.001
BPD	15	5.53	[3.72–8.20]	<0.001
MA Ds	19	4.58	[3.38–6.21]	<0.001
RCTs	8	4.29	[1.46–12.6]	0.008
Open trials	26	5.00	[3.83–6.53]	<0.001

Analyses based on conservative, random-effects modeling, with stratification.
From Baldessarini et al. 2005.

Long-term RCTS in Bipolar Disorders: *Anticonvulsants*

Studies	Dx	Mos	Other Rx	Relapse Rate (%)		RR
				AC	Other	
<i>Divalproex</i>						
Bowden et al. 2000	M	Š18	Lithium	45/187 (24.1%)	28/91 (30.8%)	1.28
			Placebo	45/187 (24.1%)	36/94 (38.3%)	1.59
Calabrese et al. 2005	RC	Š12	Lithium	14/28 (50.0%)	18/32 (56.2%)	1.12
<i>Lamotrigine</i>						
Calabrese et al. 2000	RC	Š6	Placebo	45/93 (48.4%)	48/89 (55.1%)	1.14
Bowden et al. 2003	M	Š6	Lithium	28/59 (47.5%)	18/46 (39.1%)	0.82
			Placebo	28/59 (47.5%)	49/70 (70.0%)	1.47
Calabrese et al. 2003	D	Š6	Lithium	68/221 (30.8%)	45/121 (32.2%)	1.05
			Placebo	68/221 (30.8%)	43/121 (35.5%)	1.15

Long-term RCTS in Bipolar Disorders: *Modern Antipsychotics*

Studies	Dx	Mos	Other Rx	<i>Relapse Rate (%)</i>		RR
				APD	Other	
<u><i>Olanzapine</i></u>						
Tohen et al. 2004	M/D	Š18	ONZ vs. PBO +Li/D VP	11/30 (36.7%)	21/38 (55.3%)	1.51
Tohen et al. 2005	M	Š12	Lithium	53/214 (24.4%)	69/214 (32.2%)	1.32
Ketter et al. 2006	M	Š12	Valproate	65/217 (30.0%)	83/214 (38.8%)	1.29
<u><i>Aripiprazole</i></u>						
Keck et al. 2006	M	Š6	Placebo	21/77 (27.3%)	36/83 (43.4%)	1.59

Conclusions:

Long-term mood-stabilizer treatment

- Modest effect sizes; chaotic morbidity; high dropouts; PBO difficult practically & ethically
 - Inadequate Rx of depressive/dysphoric/mixed morbidity, though disabling & lethal
 - Episode-counts less sensitive/valid than %-time-ill, & greatly underestimate slower/longer D-type morbidity
 - Benefits/risks of all Rxs poorly tested in BP-II syndrome
 - Most trials far too brief & risk relapse *not* = recurrence?
 - Rx-discontinuation artifacts very likely; optimal control by dose-tapering remains little tested with lithium, untested with others
 - Time-to-recurrence hypothesis (survival analysis) needs more testing as a surrogate for total long-term morbidity
 - “Enrichment” & “relapse-prevention” designs: surely biased, even if “necessary” for recruitment & signals?
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