ISCTM Symposium

Treatment of Bipolar Depression

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Comparison: Bipolar vs. Unipolar Depression

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Potential Conflicts of Interest
–2009–

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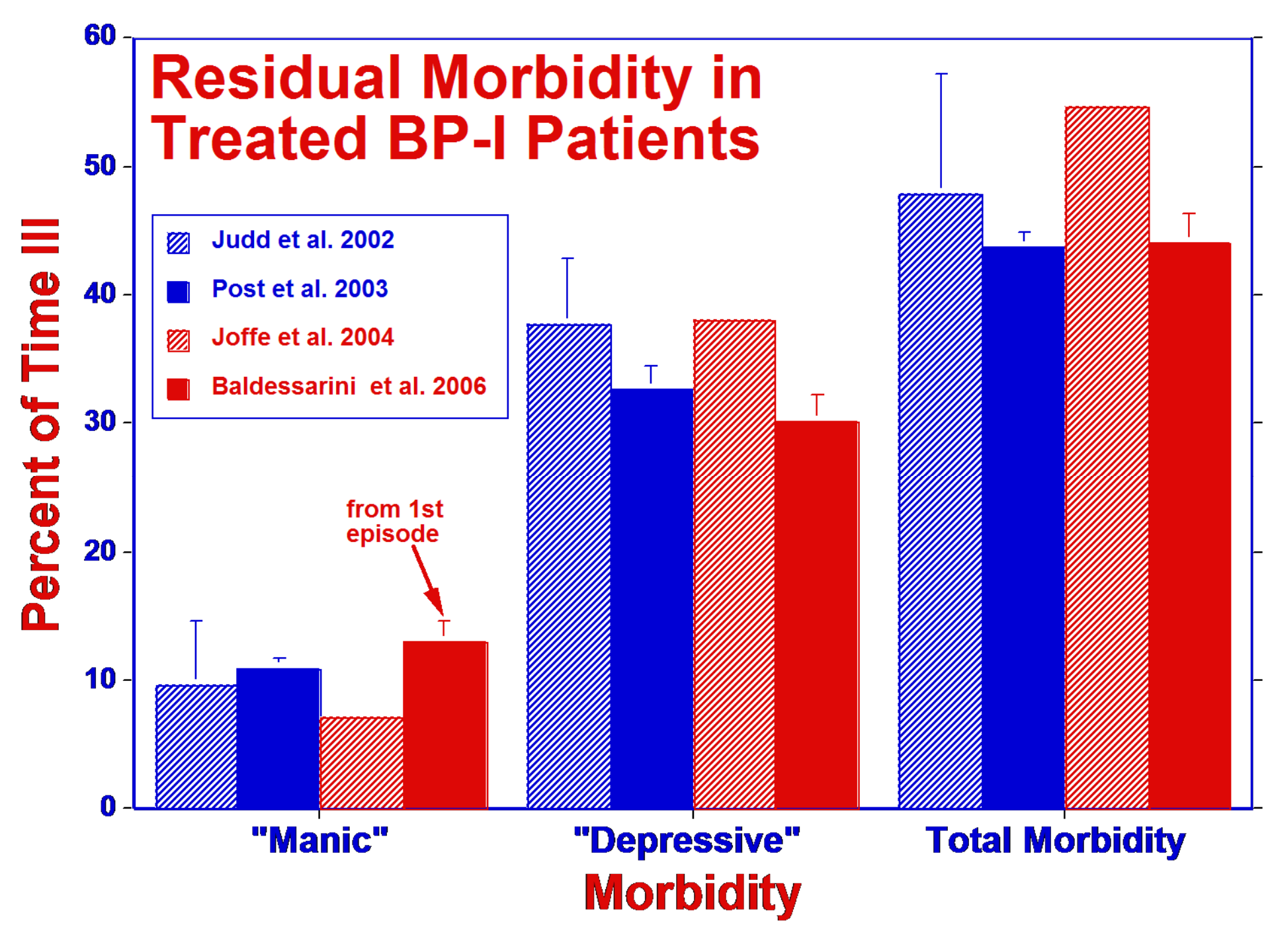
Dr. Baldessarini has been a consultant or investigator-initiated research collaborator with: AstraZeneca, Auritec, Biotrofix, Janssen, JDS-Noven, Lilly, Luitpold, NeuroHealing, Novartis, Pfizer, and SK-BioPharma Corporations. He is not a member of corporate speakers' bureaus, nor does he or any family member hold equity positions in biomedical or pharmaceutical corporations. He holds 5 unlicensed patents on novel aporphines as atypical antipsychotics, for epilepsy, stroke-recovery, or peptic ulcer, & on *l*-methylphenidate as a dopamine antagonist.

Bipolar vs Unipolar Depression: *Clinical*

- High risk: "unipolar" Dx error in early episodes (5%–10% of UP cases, but found in up to ½ of BPD cases)
- Interviewing family or friends can help
- Family history: mania, depression, psychosis, alcohol, suicidal, "breakdowns," hospitalizations
- Cyclothymic or hyperthymic temperament sometimes
- Onset: BP-I <BP-II < UP (younger esp. if familial mood disorder or suicide)
- High recurrence rate & seasonal mood/energy shifts
- Subtle mania-like features in depressions ("mixed")
- More psychomotor retardation-leaden paralysis, hypersomnia, hyperphagia, paucity of thought ("atypical" symptoms); also variable anxiety, agitation, psychosis)

BPD vs UP Disorders: *Recent Research*

- **BPD: highest long-term *Dx-stability* (>95% vs. ca. 75% MDD); Salvatore et al. *J Clin Psychiatry, Br J Psychiatry* 2009)**
- ***Earlier median onset*: BP-I (24) < BP-II (29) < UP (31 yrs); BP-I men (22) << UP-women (32 yrs; Baldessarini et al., 2867 cases. *ISCTM poster, 2009*)**
- ***Rating-scale* differences (N=2600 HDRS-21 items: *BP*: more paranoid, dysfunctional; *UP*: more somatic, hypochondriasis, insomnia, wt-loss; Tondo et al. 2009)**
- ***BPD morbidity* from onset mainly depressive & poorly controlled by Rx & predicted from onset (ill 45% of wks, 75% depressive; Salvatore et al. Epidem Psichiatr Soc, 2007)**
- ***Suicide rate* BPD >> UP; many *accidents* in youth + *late medical mortality* in both (Tondo et al. *Acta Psychiatr Scand* 2007; Khalsa et al. *J Affect Disord* 2008)**


Residual Morbidity in Treated BP-I Patients
Judd et al. 2002
Post et al. 2003
Joffe et al. 2004
Baldessarini et al. 2006
from 1st episode
Percent of Time Ill
60
50
40
30
20
10
0
"Manic"
"Depressive"
Total Morbidity
Morbidity

Depression vs. *functional* recovery: First-episode BP-I patients by 3 yrs

Status	N	% of Weeks in MDD
Recovered (39.4%)	119	17.3 ± 42.2
Not recovered (0.0%)	184	88.3 ± 19.4
Odds Ratio [95% CI]		3.01 [1.47–6.18]
		p = 0.003

Baldessarini, Tohen et al: International First Episode Project, 2006.
Recovery = regaining *baseline* occupational+locational status.

Suicidal risks vs DSM-IV diagnosis

Measures	BP-I	BP-II	MDD
Cases	529	314	1983
Years-at-risk	13.2	16.3	9.30
Rates (%/yr)			
Suicides (S)	0.14	0.16	0.05
Attempts (A)	1.52	0.82	0.48
All acts	1.66	0.98	0.53
Suicide SMR	12.8	14.7	4.59
Lethality (A/S)	10.8	5.12	9.60

From Tondo & Baldessarini Acta Psychiatr Scand 2007 (2826 Sardinians).
SMR = observed/local gen. pop. suicide rate [10.9/100k/yr]; gen. popl A/S ca. 25.
Note: Rates of acts are similar vs. Dx among ever-hospitalized patients, but BPD risk >> MDD cases of *variable* severity.

Antisuicidal effects of treatments

Clozapine

FDA-approved, schizophrenia (*not* proved re. suicide)

Lithium

Very effective in BPD (suicide, attempts), less in MDD
Very large evidence base, including RCTs
Remains off-label

Anticonvulsants

Less effective than lithium in BPD (several studies)

Antidepressants

Evidence is inconsistent and inconclusive;
May reduce risk in older MDD (not BPD) adults
Ideation decreased by AD > PBO in most adult trials
New ideation rate in depressed adults ca. 0.5%
"Suicidality" (mainly ideation) increased in juveniles

From et al Meltzer et al. Arch Gen Psychiatry 2003; Laughren FDAQ 2006; Guzzetta et al. J Clin Psychiatry 2007; Baldessarini et al. Bipolar Disord 2007, 2008; Pharmacopsychiatry 2009; Barbui et al. CMAJ 2009.

Treatment of Bipolar Depression

- Very *limited research* to guide clinical practice; less for BP-II, "spectrum," subgroups (mixed, RC), or direct comparisons
- Can *not assume BP = UP depression* therapeutics
- BPDs complicate treatment trials: often inc. *mood-stabilizers or polytherapy* as confounds
- *Antidepressants alone* have limited short-term & poor long-term efficacy in BPD; can worsen or induce switch vs. dose, esp. TCAs in adults (SRIs in children)
- Some anticonvulsants (lamotrigine, divalproex) or lithium ± an SRI are currently common choices
- Few modern *antipsychotics* have some RCT data (aripiprazole, quetiapine, olanzapine+fluoxetine: mostly short-term or add-on)
- *Prophylactic trials* in BPD: rare & often rely on narrow designs (relatively brief, confounded by *discontinuation*)

From Baldessarini & Tarazi: *Goodman & Gilman's Textbook*, 2005

Maintenance Treatment: Latency in BPD

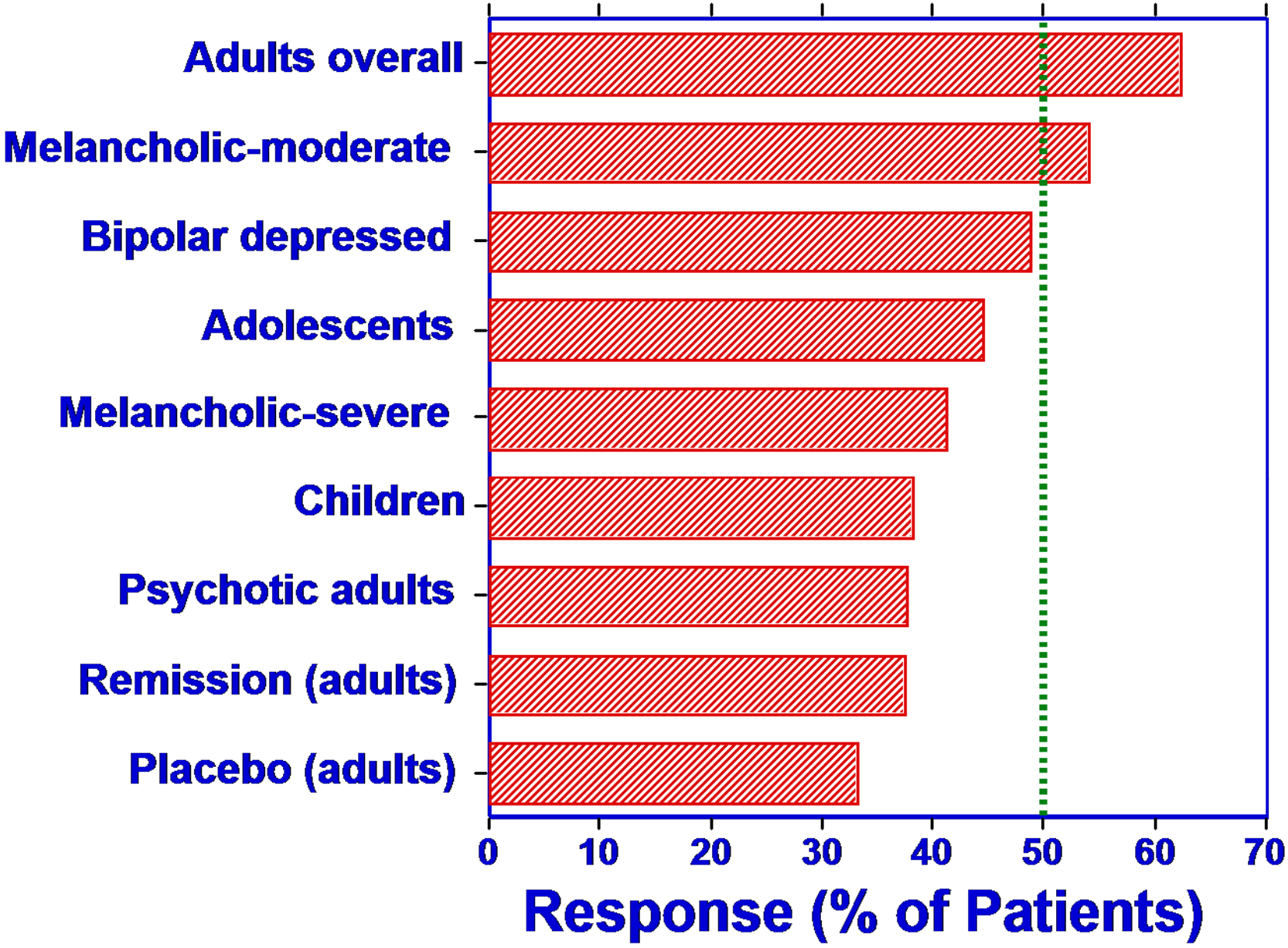
Group	Latency (years)
Bipolar II	9.8 ± 8.8
Bipolar I	7.6 ± 8.2
Women	9.2 ± 9.0
Men	7.5 ± 8.5

Re. 750 Berlin+Sardinia patients, ≥6 months.
From Baethge et al: Can J Psychiatry 2003; 48 449–457.

Treatments: Bipolar depression

Agent	*FDA-Approved Indications*
Older ADs	None (UP only; high switch-risk in BPD > age 14)
Modern ADs	UP only (widely assumed for any "depression"); moderate switch-risk in BPD (esp. < age 14)
Lithium salts	Long-term: BP-I "recurrences" (depression *not* specified; *perhaps* effective in acute BP-depression & BP-II)
Divalproex	Antimanic only (short-term), but widely used for all aspects of BPD
Carbamazepine	Antimanic only (short-term); complex drug-interactions (oxcarbazepine not approved)
Lamotrigine	Long-term only (minimally antimanic; needs time to dose safely)
Olanzapine +Fluoxetine	Short-term: BP-dep. (may not exceed FLX-alone but low mania-risk; long-term not proved)
Quetiapine	Short & long term: BP mania & dep. (BP-II pending; UP off-label)

Typical Responses to Antidepressants in MDD

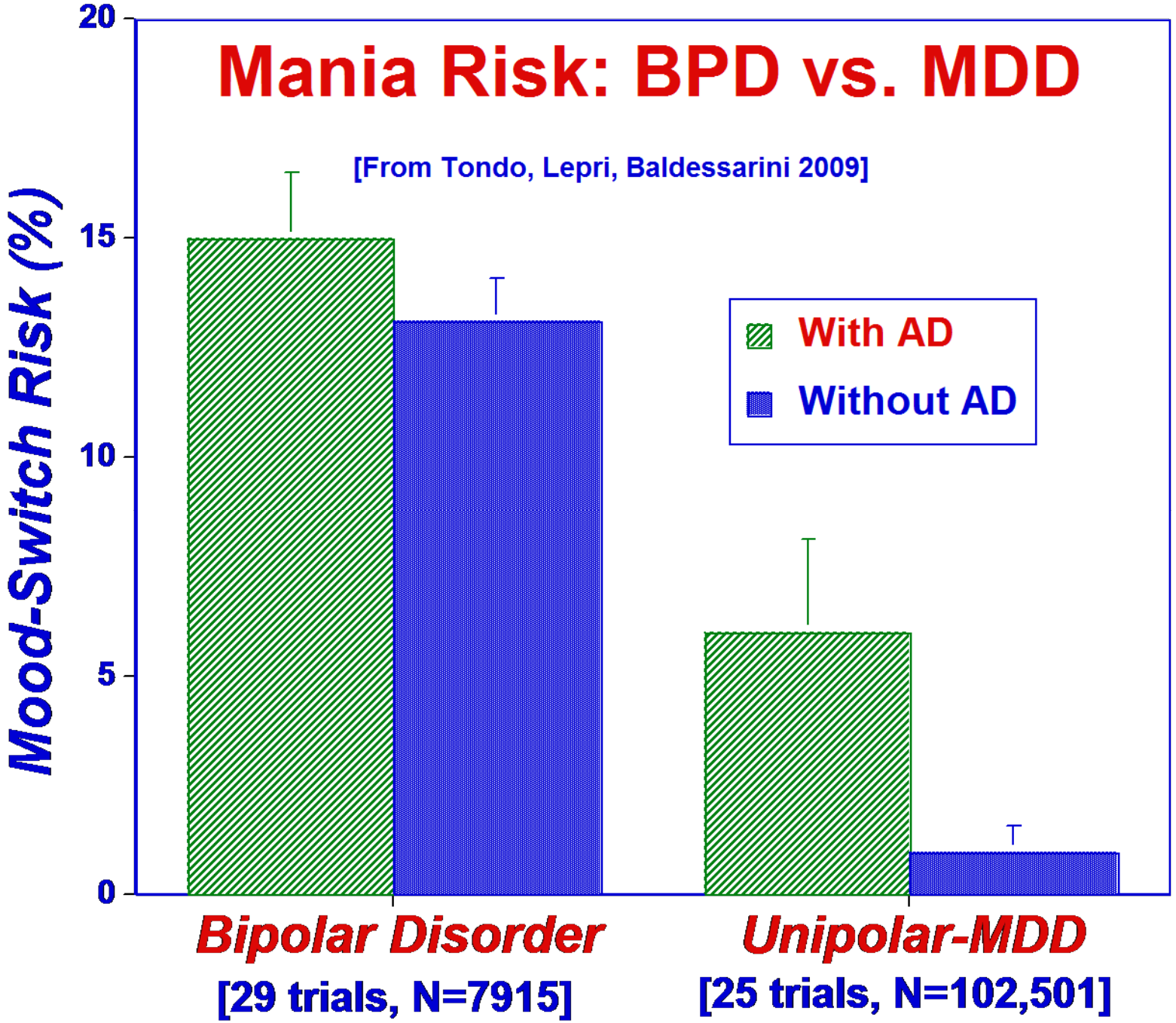


Antidepressants: Switch risks

Drug type	Trials (n)	Ss (N)	*% New Mania* [95% CI]
Mixed agents	22	3878	22.1 [21.6–22.5]
TCAs	46	10,187	12.7 [12.4–12.9]
SRIs	18	38,612	8.71 [8.59–8.83]
SNRIs	6	1361	7.77 [7.22–8.33]
Bupropion	3	69	7.63 [6.04–9.21]
MAOIs	14	2179	4.58 [4.38–4.77]
All ADs	111	56,212	12.5 [12.4–12.6]
No ADs	45	58,309	7.46 [7.36–7.56]
Relative Risk	156	114,501	1.68

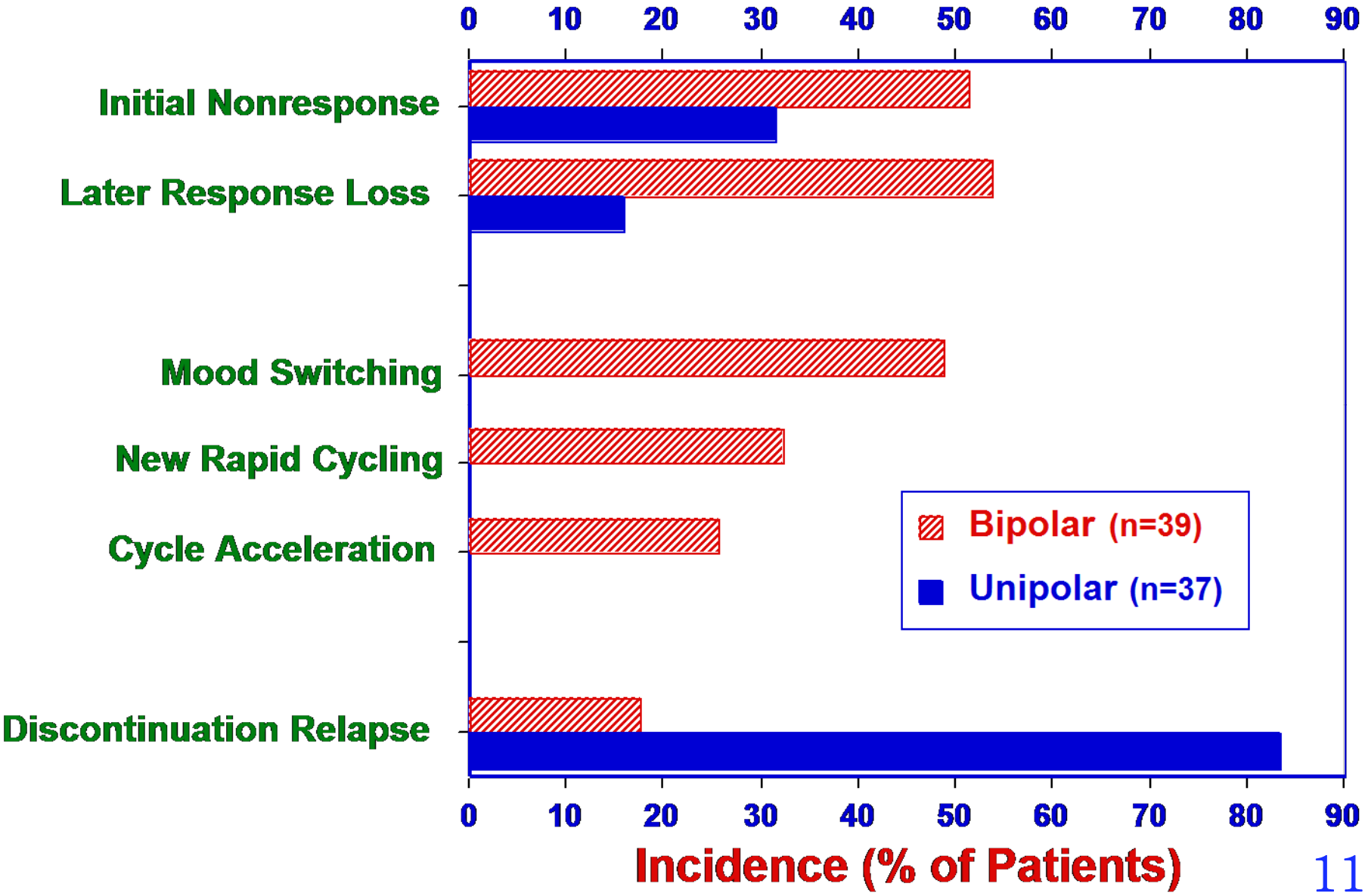
[From Tondo, Vázquez, Baldessarini 2009]. Mania includes hypomania.

[*] Based on meta-analysis. Note: use of mood-stabilizers had limited effect: among BPD, switch risk fell from 16.5% to 11.2%, but their non-randomized use may confound by illness-severity or suspected bipolarity.


Mania Risk: BPD vs. MDD
[From Tondo, Lepri, Baldessarini 2009]
Mood-Switch Risk (%)
20
15
10
5
0
With AD
Without AD
Bipolar Disorder
[29 trials, N=7915]
Unipolar-MDD
[25 trials, N=102,501]

Antidepressant Responses: BP vs. UP Depression

[Adapted from Ghaemi et al. Am J Psychiatry 2004; 161: 163–165]



Antidepressants (ADs): Acute BP-depression

Outcome	*Proportion (%)* ADs	PBO
A. Partial Response	57.1	34.1
B. Full Remission	38.4	31.2
C. Switch Risk*	6.5	4.7
True Benefit (B – C)	31.9	26.5
Net AD-Superiority	5.4%	

From Gijsman et al. Am J Psychiatry 2004; 161: 1537; & Post RM, Stanley Institute Report, 2004. [*] Low switch risk may reflect mood-stabilizer co-treatment in most cases.

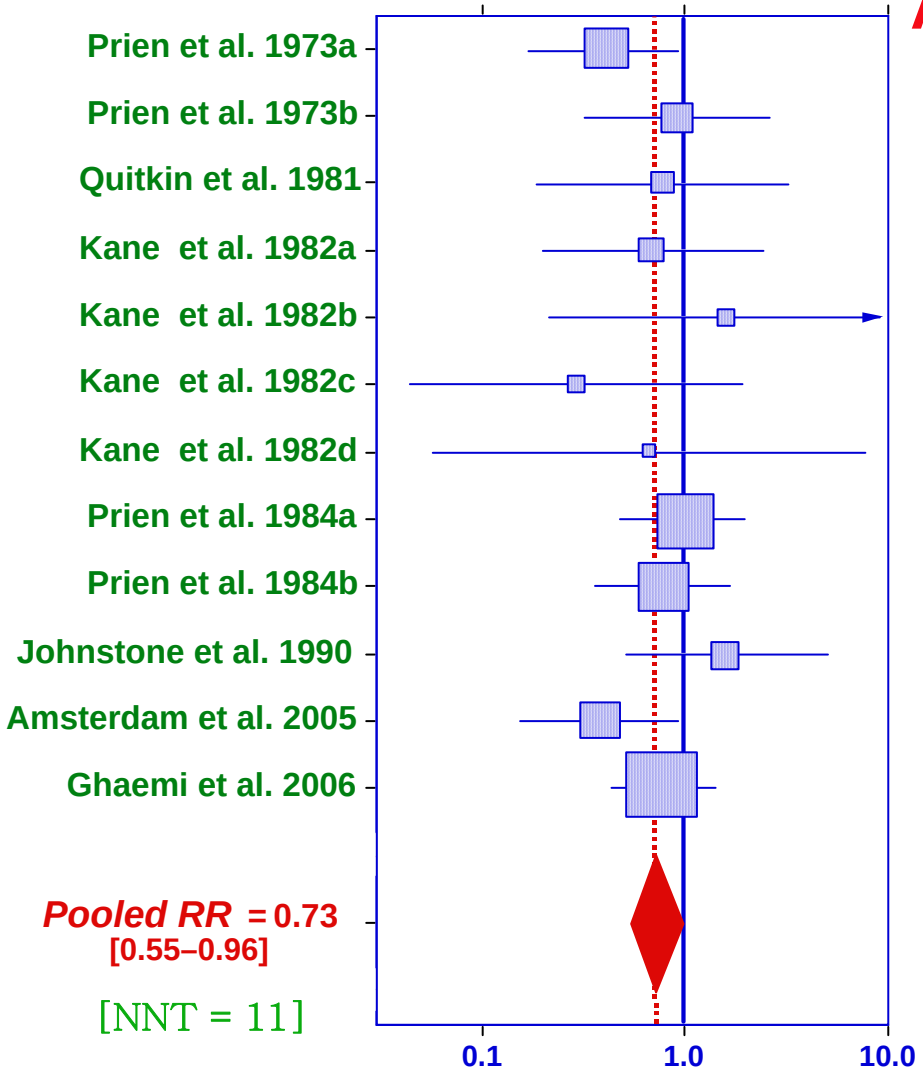
Adding antidepressants vs. placebo to mood-stabilizers in BP-depression

Outcome	MS+PBO	MS+AD	*p*
Remission	51/187 (27.3%)	42/179 (23.5%)	0.40
Switch	59.153 (38.6%)	67.157 (42.7%)	0.46

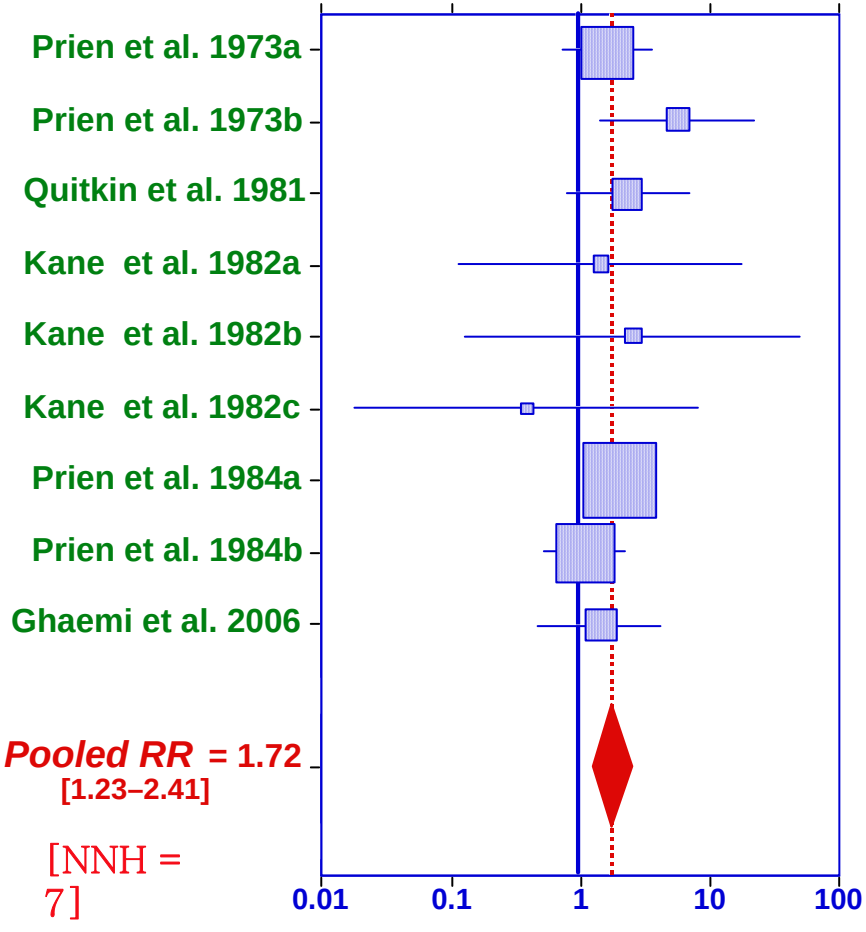
RCT to 26 weeks, mood-stabilizer (MS)+paroxetine or bupropion or +placebo. MSs = *anticonvulsants* (VPA >> CBZ; 45.8%), *lithium* (39.1%), or modern *antipsychotics* (15.1%). From Sachs et al. N Eng J Med 2007; 356: 1711–1722. Others found adding AD vs. second MS similar (e.g., Young et al. Am J Psychiatry 2000; 157: 124–126).

Meta-analyses: Long-Term Antidepressant Trials in BPD

[Ghaemi et al. Acta Psychiatr Scand 2008:118:347–356]



Depression



Mania

Randomized 12-mo trial: Mood-stabilizer ± AD after acute BP dep.

Outcome Measure	*Antidepressants* *Continue*	*Stop*	*Change with AD*	*p*
% Wks Ill/year				
Depression	76.2±25.3	80.5±15.3	–5.3%	<0.05
Mania-hypo	50.5±29.5	41.7±33.5	+21.1%	NS
Wks to Recurrence				
Depression	41.4±3.0	31.5±3.3	+31.4%	<0.05
Mania-hypo	45.2±2.8	47.0±2.3	–3.8%	NS

Nonblinded, trial with 24 patients/arm recovered (3 mos) from acute dep, episode with a modern AD+mood-stabilizer. Benefits of continued-ADs are small; limited mania-risk with ADs but questionable prophylaxis by mood-stabilizers. From Ghaemi et al. 2009.

Initial prescriptions for 14,000 BPD patients (US)

Drugs	% of Patients
Monotherapies	
Antidepressants	61.1
Anticonvulsants	8.71
Antipsychotics	7.61
Lithium	2.99
All monotherapy	**80.4**
Polytherapies	
Mood-stabilizer + antidepressant	6.27
Antipsychotic + antidepressant	6.14
≥3 Drugs	4.09
Mood-stabilizer + antipsychotic	3.12
All Polytherapy	**19.6**
Total Antidepressants	**≥75.0**

From Baldessarini et al. Psychiatr Serv 2007 & 2008. Later changes almost always involved *adding* another drug (polytherapy).

Duration: Initial monotherapy in 7000 US BPD patients

Treatment	Median Days Used
Lithium	200
Antidepressants	140
Anticonvulsants	90
Antipsychotics	90
Sedatives	65

From Baldessarini RJ, et al.: Psychiatr Serv 2007; 58: 85–91.
Differences are highly statistically significant

Conclusions: Bipolar Depression

- A most important clinical & public-health challenge
- Often misdiagnosed as unipolar
- Latency to maintenance-Rx, 5–10 yrs (longer BP-II, women)
- Depression-dysthymia-dysphoria: predicted from onset; remain major *uncontrolled treated* morbidity in BPD
- Increases disability, alcohol-abuse, & mortality (suicide+ accidents early; excess medical deaths later)
- Treated poorly by antidepressants TCAs best but risky), inadequately by mood-stabilizers
- Switch risk 5%–15% (TCAs adult, SRIs children); may be little-reduced by mood-stabilizers
- Suicide risk: reduced with lithium > anticonvulsants