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Long-Term Drug Efficacy in Major Psychiatric Disorders: *Problems & Opportunities*

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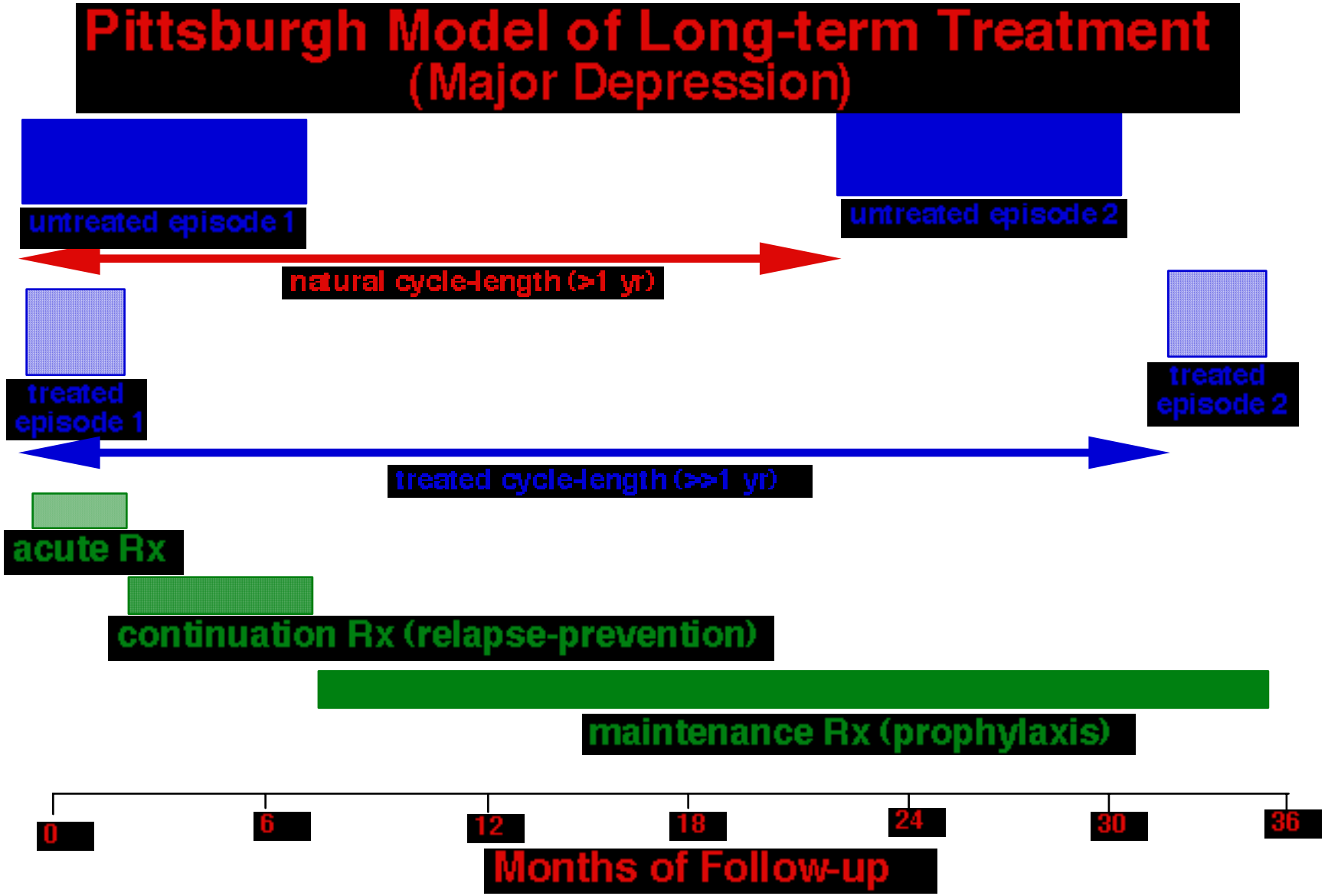
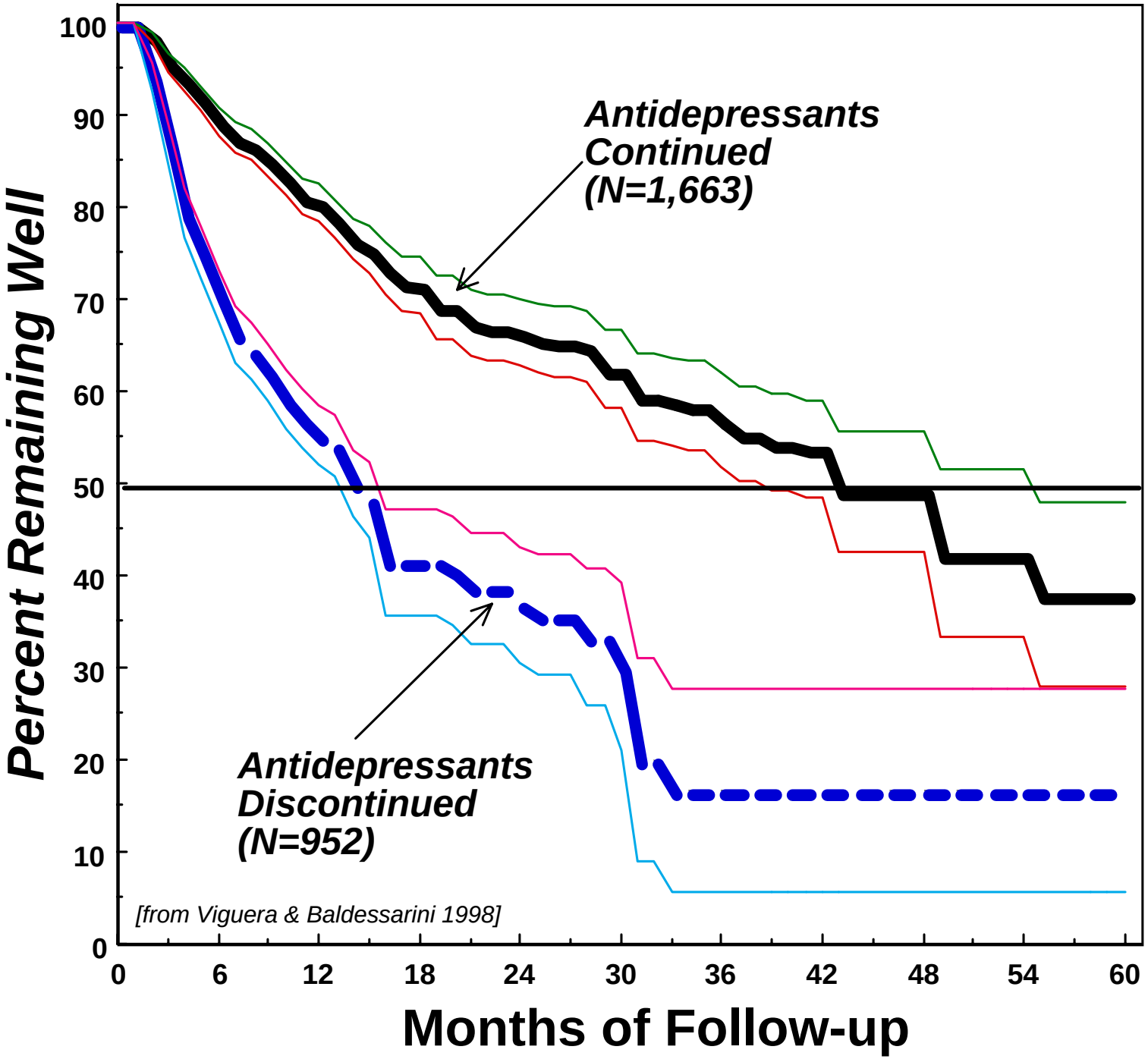
Topics to be discussed

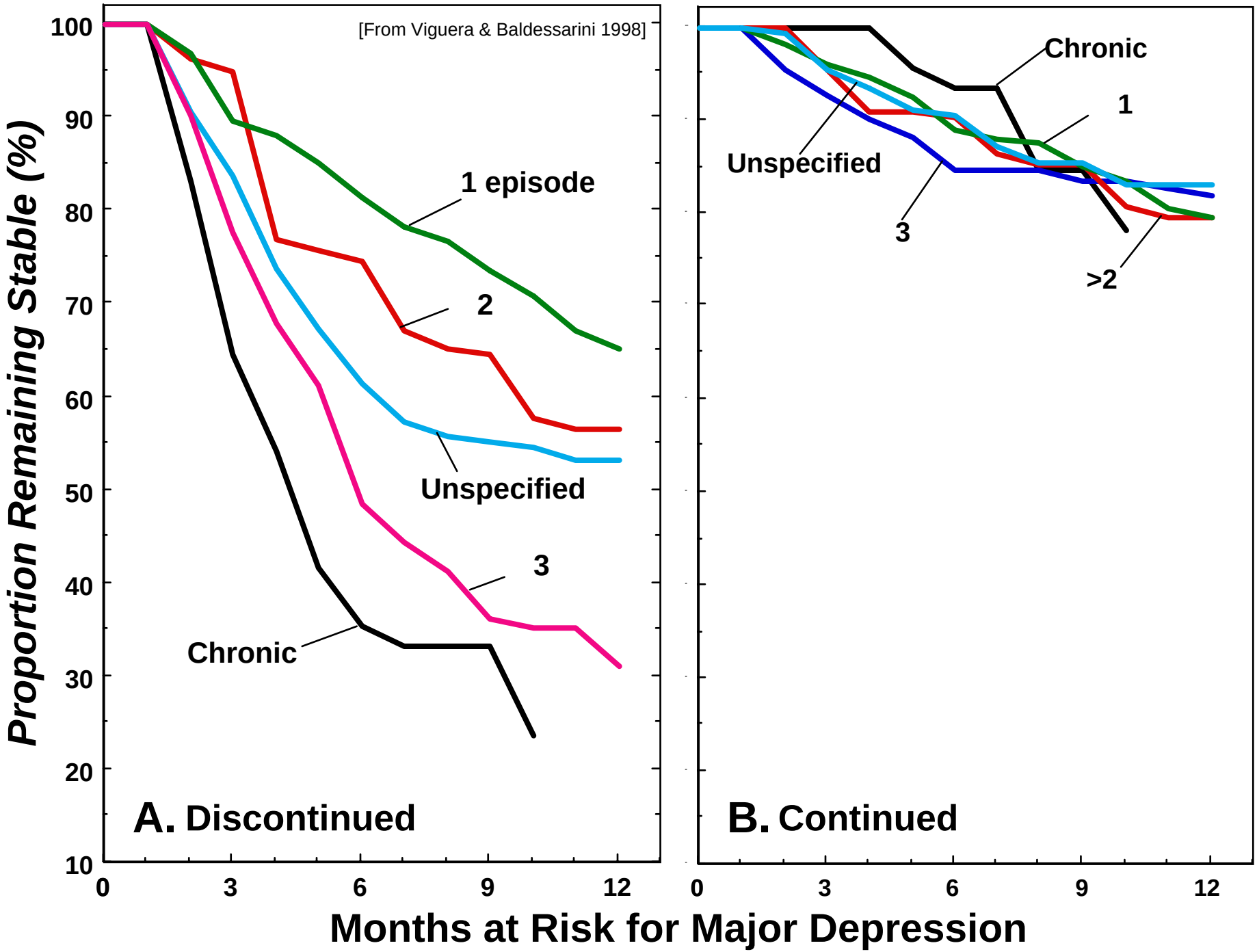
- Conceptual issues for testing long-term/maintenance/ prophylactic treatments for major mental illnesses
- Integrating clinical/pharmacological/statistical/industrial regulatory/social interests: *Kety's famous dancing bear at the Russian circus: It is not a matter of how well he does it, but that he does it at all!*
- Nature & treatment of major depression & other uses of "antidepressants"
- Nature & treatment of schizophrenia/psychotic disorders
- Nature & treatment of bipolar disorders (more to follow)
- Summary of reality-checks about what has been done & needs to be done in this area
- Issues for discussion during this ISCTM symposium on long-term trials methods

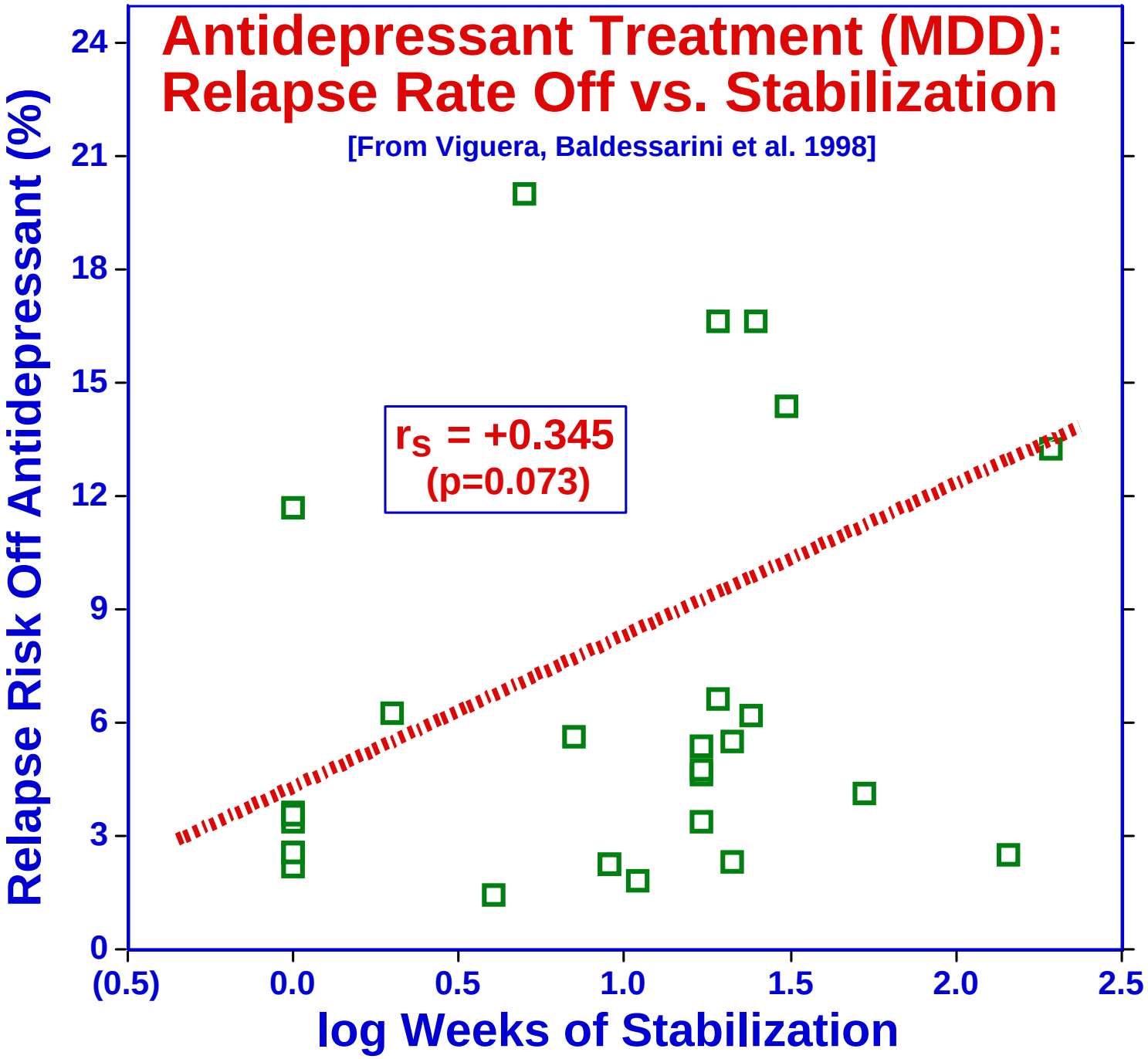

Pittsburgh Model of Long-term Treatment
(Major Depression)
untreated episode 1
untreated episode 2
natural cycle-length (>1 yr)
treated episode 1
treated episode 2
treated cycle-length (>>1 yr)
acute Rx
continuation Rx (relapse-prevention)
maintenance Rx (prophylaxis)
0
6
12
18
24
30
36
Months of Follow-up

Major Depressive Disorder:
Characteristics of Illness & Treatment

- Acute untreated episodes: 3–9 mos, vary with age
- Slowly recurrent (typically <1/year) ± chronic dysthymia
- May be >1 disorder: overlaps BP-II, high cultural variance
- Prevalent comorbidity, disability, & poorly studied mortality
- Psychosis varies with severity (poorly studied with modern Rxs)
- Most Dxs missed/delayed; Rx brief with low doses (esp. I°-care)
- Short-term Rx benefits often marginal vs. placebo
- Long-term effects poorly/briefly studied with modern agents
- Long-term effects poorly predicted by past history
- Survival-analysis unvalidated as long-term morbidity surrogate
- Long-term Pbo: ethical-IRB/recruitment/retention problems
- Trials follow Pittsburgh "continue–maintain" model
- Discontinuation artifacts likely & may *worsen* with longer Rx
- Long-term antidepressant benefits in other Dxs (inc. BPD) uncertain
- Long-term dosing requirements untested in any Dx

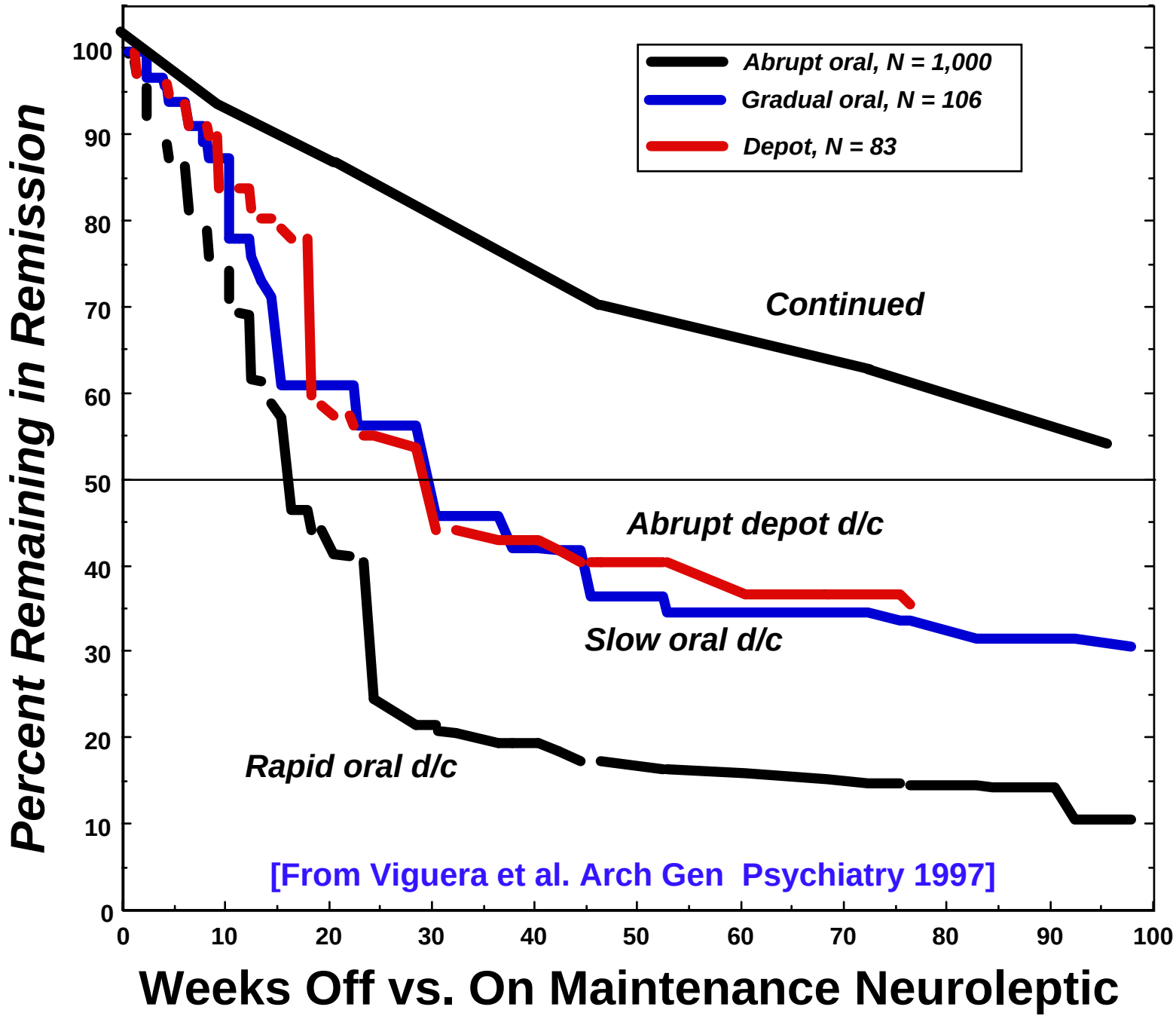

Percent Remaining Well
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
30
36
42
48
54
60
Months of Follow-up
Antidepressants
Continued
(N=1,663)
Antidepressants
Discontinued
(N=952)
[from Viguera & Baldessarini 1998]


[From Viguera & Baldessarini 1998]
Proportion Remaining Stable (%)
100
90
80
70
60
50
40
30
20
10
1 episode
2
Unspecified
3
Chronic
A. Discontinued
Chronic
1
Unspecified
3
>2
B. Continued
0
3
6
9
12
0
3
6
9
12
Months at Risk for Major Depression

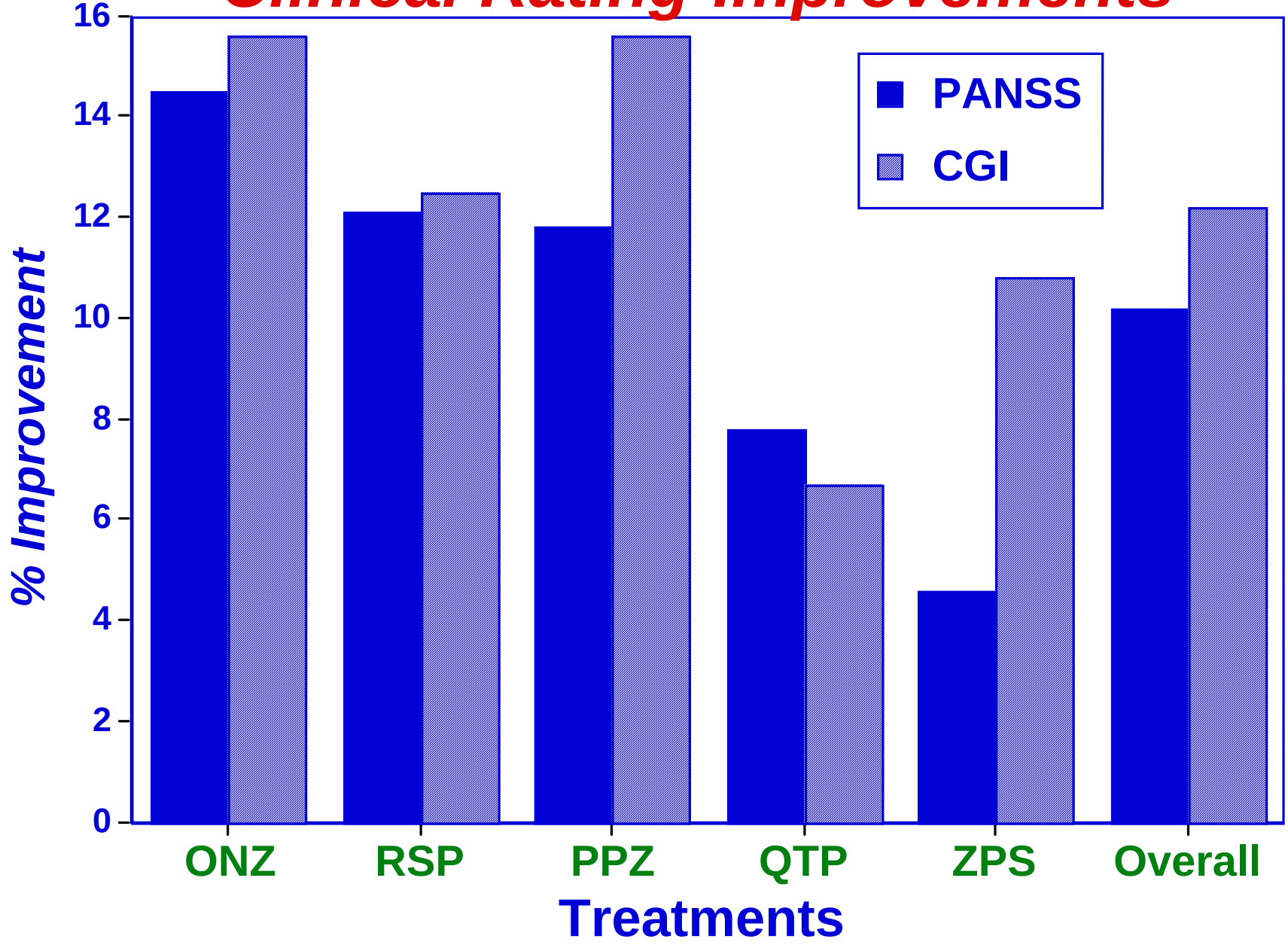

Antidepressant Treatment (MDD):
Relapse Rate Off vs. Stabilization
[From Viguera, Baldessarini et al. 1998]
r_S = +0.345
(p=0.073)
Relapse Risk Off Antidepressant (%)
log Weeks of Stabilization
24
21
18
15
12
9
6
3
0
(0.5)
0.0
0.5
1.0
1.5
2.0
2.5

Psychotic Disorders:
Characteristics of Illnesses & Treatment

- Schizophrenia: chronic+erratic fluctuations, stress-sensitive
- Prevalent dementia, disability & some mortality
- Other psychoses poorly studied (delusional, affective, brief)
- Long-term treatment effects very small in schizophrenia
- Long-term inter-drug differences ±trivial (except CLZ)
- Long-term drop-out rates very high
- Retention-time: an outcome measure-of-despair?
- Most trials far too short: >2 yrs to 50%"relapse" off-Rx
- Long-term Pbo: controversial ethically/clinically
- Treatment carry-over & discontinuation artifacts abound
- Washouts may require weeks or months, not days
- Core negative Sx & cognition hard to assess, harder to treat
- Long-term Rx options & combos: lack corporate interest
- Symptom-scales dominate outcomes
- Crucial functional/QOL outcomes remain "side-issues "


Abrupt oral, N = 1,000
Gradual oral, N = 106
Depot, N = 83
Continued
Abrupt depot d/c
Slow oral d/c
Rapid oral d/c
[From Viguera et al. Arch Gen Psychiatry 1997]
Percent Remaining in Remission
0
10
20
30
40
50
60
70
80
90
100
Weeks Off vs. On Maintenance Neuroleptic

CATIE Study:
Clinical Rating Improvements



Bipolar disorders:
Characteristics of Illnesses & Treatment

- Irregularly episodic, chaotic, unstable+lesser-chronic
- Untreated episodes: Mania: 3–6, Depr: 4–10 mos
- Many mixed-episodes in types I & II (often missed)
- Psychosis common in BP-I (unevenly studied)
- Hypomania often undiagnosed/misdiagnosed
- High comorbidity/disability/*mortality* (inc. BP-II)
- Therapeutics of BP-II & Mixed-states poorly studied
- Residual-*treated* morbidity: depressive >> manic
- Severe dysfunction & cognitive deficits in BP I & II
- Very high substance & anxiety disorder comorbidity
- Very high all-cause mortality in I & II (poorly studied)
- Major acute treatment effects; long-term trials too short
- Relapse risk highly sensitive to Rx-discontinuation
- Enrichment/withdrawal designs can mislead

Conclusions –A:
Psychotropic *treatment-discontinuation*

- Early relapse/recurrence risk (3–6 mos) ↑↑ (artifact)
- Clearest with long-term lithium (in BPD) & old neuroleptics (in old "schizophrenia"), inc. abrupt > gradual DC
- Untested with modern schizophrenia & antipsychotics, but is typical of CLZ
- Suspected with antidepressants (TCAs in MDD); effect of abrupt/gradual discontinuation remains untested
- Discontinuation effects: plausible but untested in same trial with modern antipsychotics/anticonvulsants in mood Dxs
- Effect of treatment duration untested but ↑ risk with *longer* Rx suggested with older antidepressants
- Optimal tapering time: untested for any Rx: 2–4 wks may be *minimal* to ↓ but not eliminate risk

Conclusions –B:
Long-term treatment *design problems*

- Study design should relate to natural history of specific untreated illnesses: may need yrs not mos
- Chronic illnesses (psychotic, anxiety) may tolerate shorter trials than episodic (mood) disorders
- Enrichment+discontinuation designs now standard in most disorders, but risk discontinuation artifacts
- Carry-over effects can arise in parallel-groups as well as cross-over designs
- Hard to avoid Rx-discontinuation effects: change of agent or to Pbo; cross-protection across drugs not tested
- Longer stabilization may not solve, or may even worsen discontinuation artifacts ("dependency" model)

Conclusions –C:
Long-term treatment *design problems*

- Assumption that early relapse prevention (<12 mos) predicts long-term prophylaxis is untested
- Assumption that time-to-first-recurrence ("survival analysis") predicts true prophylaxis is untested
- Placebo → major ethical/clinical/IRB/enrollment/ retention challenges & maximizes discontin. artifacts
- High dropout rates (30%–80%): "one year" trials are really more like six-month trials
- Very long trials constrained by ethics/feasibility/ subject-retention/cost
- Multi-site & off-shore trials risk site-variance & unknown cultural variance for Dx & assessment

Conclusions –D:
Long-term treatment design problems

- Effect-enhancement by morbidity-enrichment: essential for enrollment (unmotivated if well), but severe/frequent illness creates conflicts
- Effect-enhancement by initial response to new products ("deck-stacking") ↑ regulatory approval ↓ generalizability
- Effect-enhancement by discontinuation ("relapse-prevention") can ↓ enrollment/retention/IRB approval, & → artifacts
- Depression model: acute/continuation (vs. relapse)/maintenance (vs. recurrence) may not apply to other Dxs (chronic psychoses, polymorphic BPD, anxiety disorders)
- Add-on trials (novel-Rx vs. Pbo): common in epilepsy research; enhance enrollment/retention; lower effect size; need to limit Rxs
- Dose-response trials: can avoid Pbo, but hard to do; need taper
- Trials of Rx-options (if A, try B): needed clinically, but conflict with commercial interest if competitors' products compared

Conclusions –E:
Long-term outcome problems

- Outcome by major illness event rates/latencies: popular technically, clinical relevance questionable
- Subsyndromal morbidity important, prevalent, rarely rated as outcome measure
- Outcome by symptom ratings: risk cultural-specificity & limited clinical relevance
- Outcome by remission, recovery or %-time well/ill : more realistic; can enhance power & shorten trials
- Outcome by functional improvement/patient-opinion: clinically relevant but far less developed technically