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

Ross J. Baldessarini, M.D.

Professor of Psychiatry & Neuroscience
Harvard Medical School
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
**Major Depressive Disorder:**
Characteristics of Illness & Treatment

- Acute untreated episodes: 3–9 mos, vary with age
- Slowly recurrent (typically <1/year) ± chronic dysphoria
- 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
Antidepressants Continued (N=1,663)

Antidepressants Discontinued (N=952)

[from Viguera & Baldessarini 1998]
Proportion Remaining Stable (%) vs Months at Risk for Major Depression

From Viguera & Baldessarini 1998

- A. Discontinued
  - Chronic
  - 1 episode
  - Unspecified

- B. Continued
  - Chronic
  - >2
  - 3

Months at Risk for Major Depression

Proportion Remaining Stable (%)
Antidepressant Treatment (MDD): Relapse Rate Off vs. Stabilization

[From Viguera, Baldessarini et al. 1998]

\[ r_s = +0.345 \quad (p=0.073) \]
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

Percent Remaining in Remission

Weeks Off vs. On Maintenance Neuroleptic

[From Viguera et al. Arch Gen Psychiatry 1997]
CATIE Study: Clinical Rating Improvements

- ONZ
- RSP
- PPZ
- QTP
- ZPS
- Overall

% Improvement

Treatments

PANSS

CGI
**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 discontinuation 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”) \( \uparrow \) regulatory approval \( \downarrow \) generalizability
- **Effect-enhancement by discontinuation** (“relapse-prevention”) can \( \downarrow \) enrollment/retention/IRB approval, & \( \Rightarrow \) 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