Multistate Outcome Analysis of Treatment MOAT

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Presented with Fond Memories of an

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Design contributors to low generalizability of maintenance studies

- **Monotherapy regimens, which are generally less effective than combinations (Geddes 2010)**
- ***Enriched* adjunctive regimens which report low completion rates**
- **Kaplan Meier Survival analysis, which reports o*nly* time to event (the when) such as drop out, but does not provide data on *whether* the event occurred**

Turner et al N Engl J Med 2008;358:252,
Suppes et al Am J Psychiat 2009;166:476

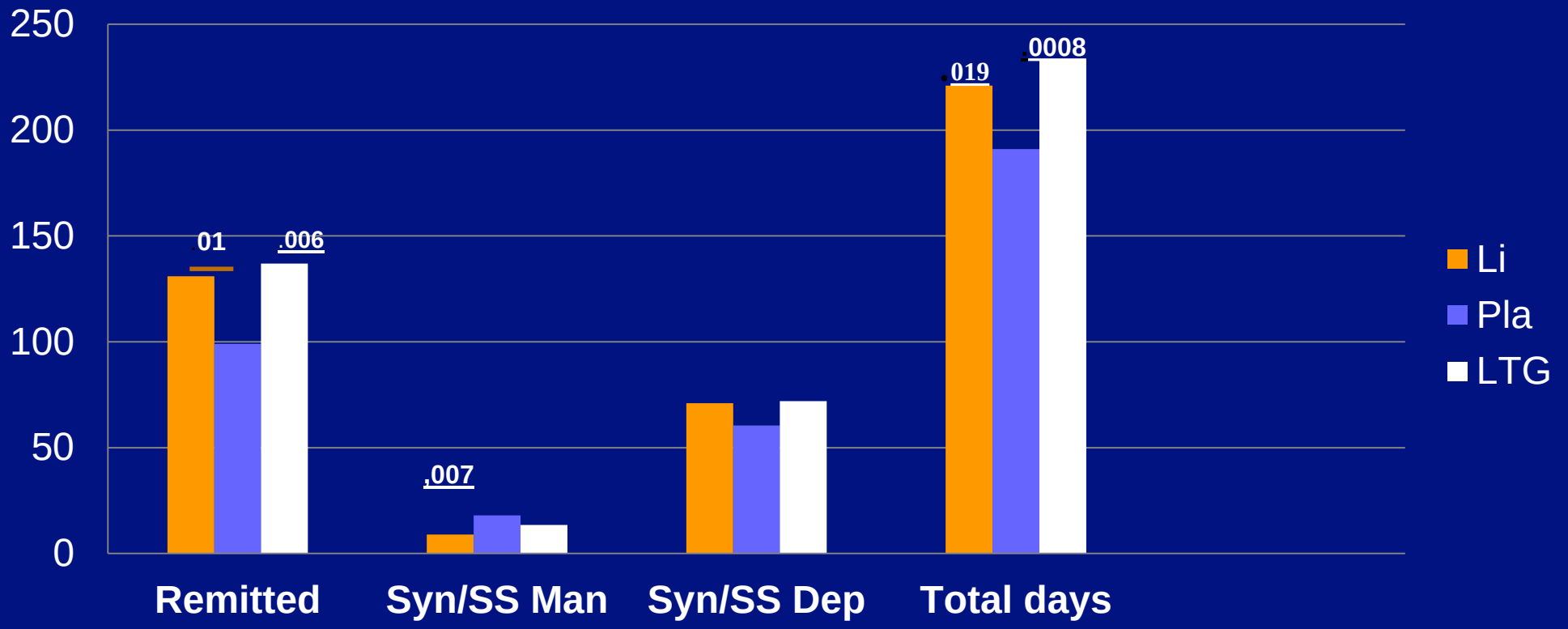
Multistate Outcome Analysis of Treatment in Bipolar Disorder (MOAT-BD)

- Total time spent on drug is partitioned into distinct mood states.
- Yields remitted, syndromal and subsyndromal manic, depressed, and mixed states
- Estimates total duration in days spent in each mood state by medication group.
- Provides quantities and *quality* of time.

NIMH : RC1MH088431

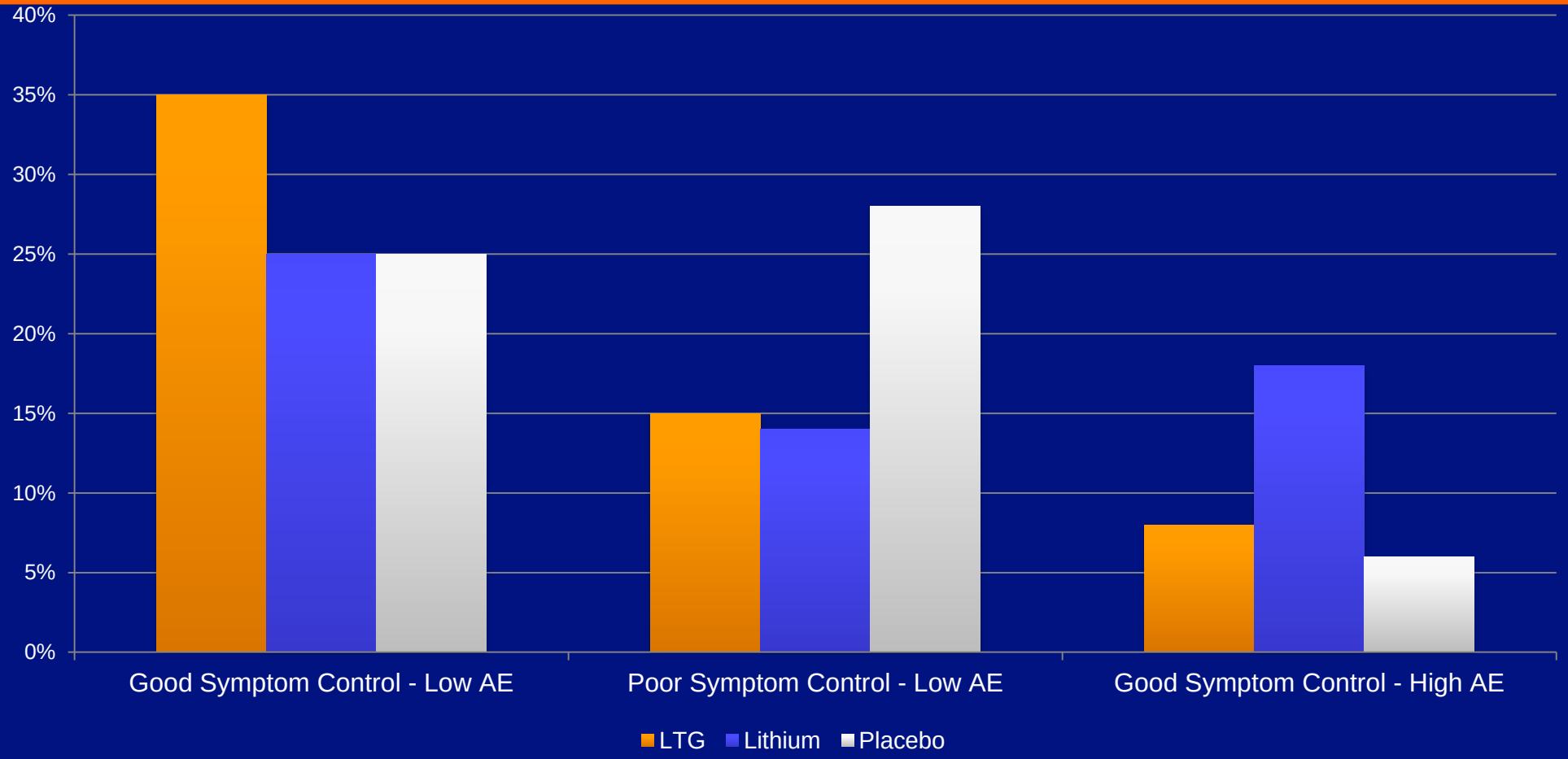
MOAT Estimates of Mean State Durations

Combined Analysis of LTG, Li and Pla in Manic and Depressed Patients Sample: 578



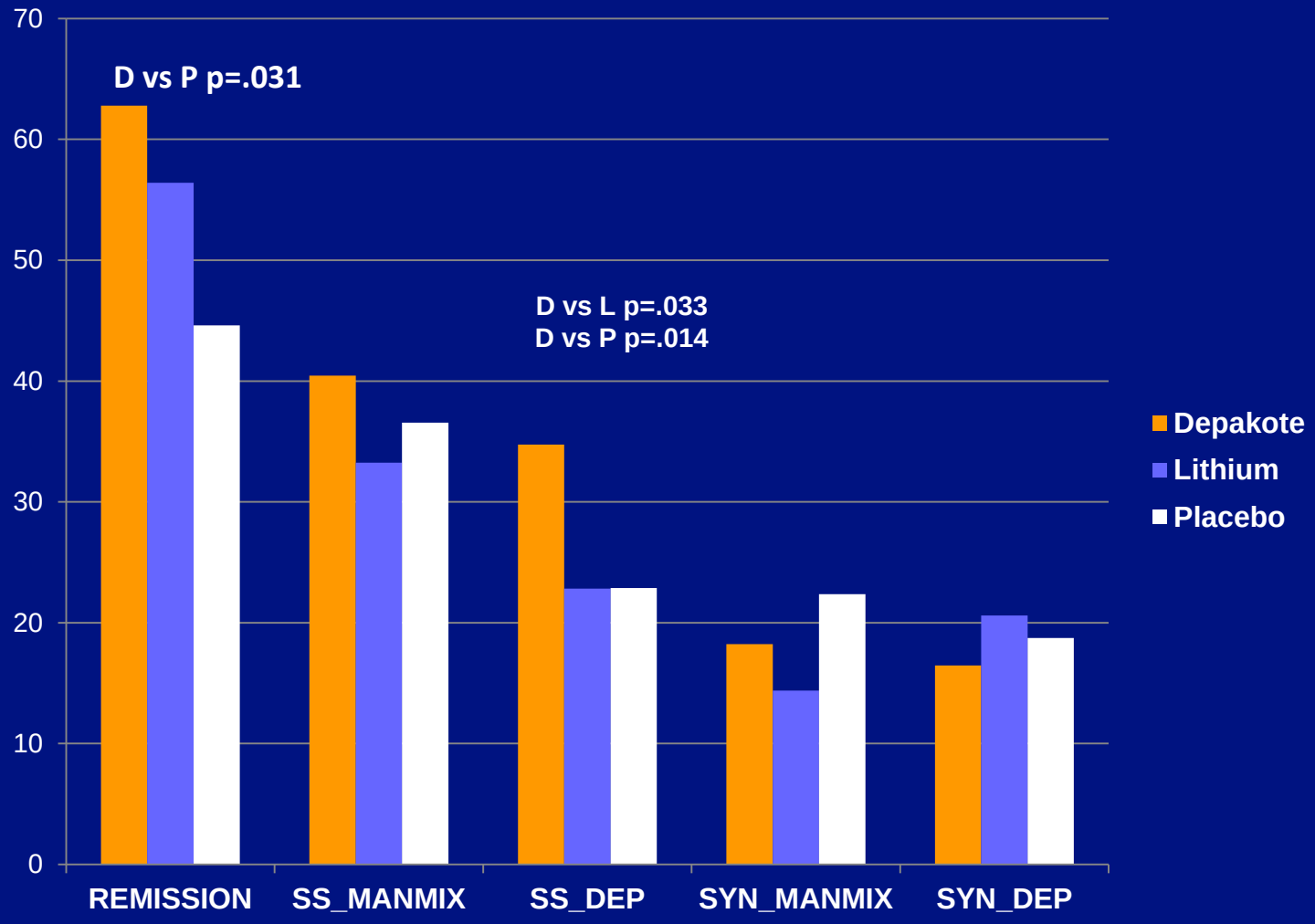
Bowden C, Tohen M, Mintz J, Molecular Psychiatry 21;237-242; 2016

Integrating MOAT symptom states and tolerability by latent class analysis



Bowden C, Tohen M, Mintz J, Molecular Psychiatry 21;237-242; 2016

Divalproex-Lithium-Placebo 12 mo. Study
https//tango.uthscsa.edu/moat



Guidelines for Combination Treatment of Mania

- If manic symptomatology persists or develops with a partially successful drug, add a second antimanic drug
- Good evidence for adding an antipsychotic to lithium or valproate or valproate to an antipsychotic in mania
- Carbamazepine least suitable due to drug interactions
- Lithium consistently least well tolerated drug
- Mood instability, not syndromal mania, is the predominant symptom requiring mood stabilizers

Tohen M, Bowden C, et al. *Br J Psychiatry*. 2008;192:135-143. Stoll A et al J Clin Psychiat 57;356, 1996; Malhi et al Bip Disord 2014: 16:455-70, Skjelstad DV et al. J Affect Disord 2010:1-13

Valproate-Lamotrigine Bipolar Depression Study Conclusions

- **Mood instability is a core component of bipolar depression, not only manic states, and is not effectively treated by lamotrigine monotherapy.**
- **Valproate plus lamotrigine reduced abrupt depressive worsening in maintenance treatment of bipolar depression.**
- **Study designs that retain high proportions of subjects allow insights into illness course and drug effects lost in standard survival analyses and LOCF imputation.**

Singh et al, 127: 145 Acta Psychiatrica Scand. 2013

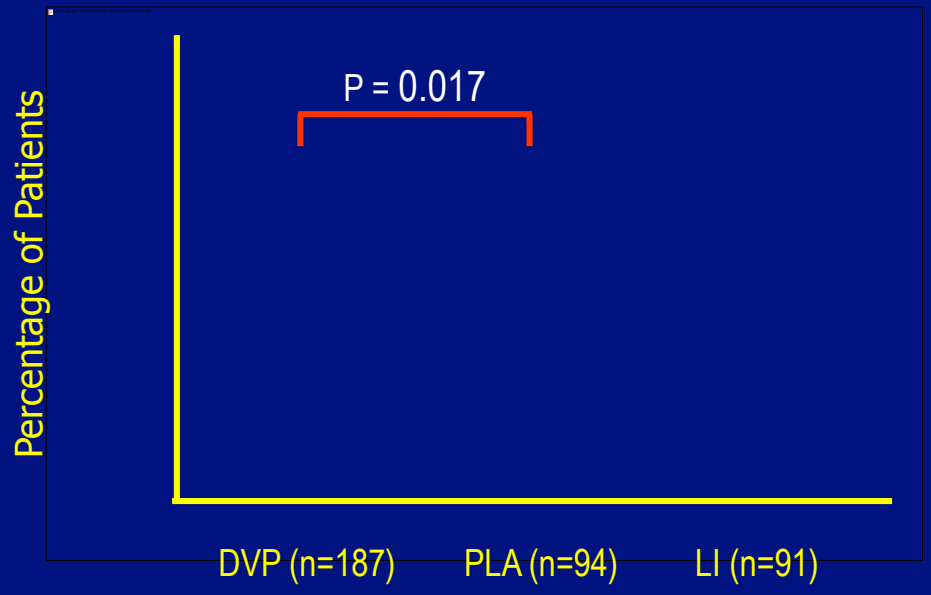
Bowden et al Acta Psychiatr Scand 2012: 126: 342–350

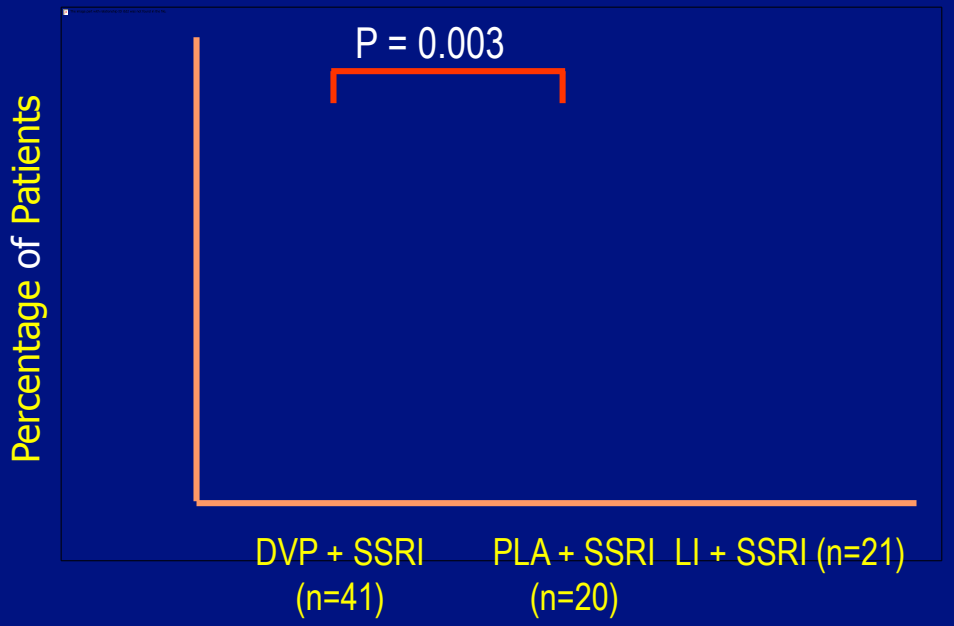
Negative Results with SSRIs in Bipolar Depression

- Paroxetine less effective than QTP, more associated with switching
- Adjunctive paroxetine or imipramine no better than Li alone.
- Meta-analysis of all types of antidepressant studies showed moderate reduced risk of recurrent depression (0.73) but increased risk of switch to manic episode (1.72)

Frye M. N Engl J Med 2011;364:51-9

Divalproex + SSRI superior to SSRI in BP I pts who developed depression in 1 yr study





PLA = placebo
DVP = divalproex

LI = lithium
SSRI =paroxetine or sertraline

Gyulai et al *Neuropsychopharmacology* 2003, 28:1374

STEP-BD and Antidepressant Use

- Antidepressants did not adjunctively benefit mood stabilizers (MS) for depression
- Adding antidepressants increased manic symptoms 3 months later
- Even in pts responding initially to antidepressants added to MS, 1-3 year depressive or manic outcomes were not better with continuation of the AD

Sachs G et al NEJM 356: 1771. 2007. Ghaemi S et al J Clin Psychiat 71:372. 2010.
Goldberg J et al. Am J Psychiat 164:1348. 2007.

Bipolar Disorder is Dimensional and Shifting in Severity Over Time

- **Depressive symptoms (32%) more frequent than manic/hypomanic symptoms (9%) or mixed (6%)**
- **Subsyndromal more frequent than syndromal symptoms (30% vs 11%)**
- **Bipolar-I patients changed symptom status an average of 6 times per year**
- **Bipolar disorder is dimensional both in severity and symptom mix.**

Judd LL et al, Long-term Natural History of Weekly Symptomatic Status of Bipolar I Disorder *Arch Gen Psychiatry. 2002;59:530*

MOAT-BD RESULTS

- Both Li and Lam provide partial benefits, increasing time remitted and overall time in study
- Neither Li or Lam reduce time depressed. 32% and 31% respectively of total time in study is spent subsyndromally or syndromally depressed
- Li superior to placebo for time spent in remission of mania, but when analysis combining tolerability is applied, loses a major part of its advantage
- In summary, Lam was associated with some therapeutic benefit but not harm; Li with benefit and harm; and placebo with neither benefit nor harm

Factor Analysis of Lamotrigine Impact in 3 Registration Bipolar Depression Trials

- Lamotrigine more effective than placebo for depressive cognitions and psychomotor slowing
- **Depressive cognitions**: mood, guilt, suicidal thoughts, helplessness, hopelessness, worthlessness (HAMD)
- **Psychomotor slowing** : psychomotor retardation, retardation-psychic, retardation-motoric items
- Lam did not benefit insomnia, somatic complaints, anxiety, insomnia, irritability

Mitchell, Hadzi-Pavlovic, Bowden et al, Current Psychiatry 18:214-24 2013

Summary of Drugs and Studies

- Keeping a patient in treatment is a fundamental goal for long term benefit
- Many drugs have evidence of antimanic effects
- Few drugs have evidence of depression and maintenance benefits
- Tolerability differs substantially among drugs