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Presented with Fond Memories of an Outstanding Statistician and Investigative Scientist

Andy Leon
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 only time to event (the when) such as drop out, but does not provide data on whether the event occurred

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

REMSSION  SS_MANMIX  SS_DEP  SYN_MANMIX  SYN_DEP

D vs L p=.033
D vs P p=.014
D vs P p=.031
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

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.

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)

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

Bipolar Disorder is Dimensional and Shifting in Severity Over Time

- Depressive symptoms (32%) more frequent than manic/hypomaniac 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*
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

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