



Who will benefit from antidepressants in the acute treatment of bipolar depression? A follow up observational data analysis of STEP-BD

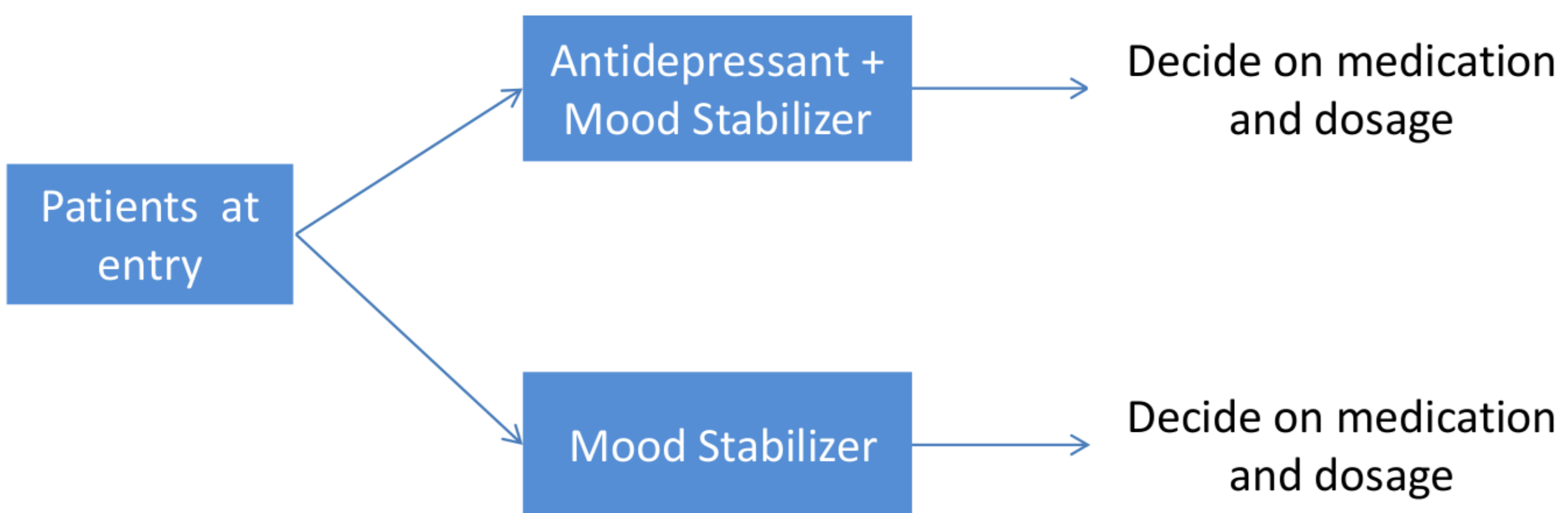
Fan Wu¹, Eric B. Laber¹, Ilya A. Lipkovich², Emanuel W. Severus³
North Carolina State University¹; Quintiles²; University Hospital Carl Gustav Carus, TU Dresden³

STEP-BD Study and SAD data

- ▶ Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD): 4,360 participants with bipolar disorder in USA from 22 sites over 7 years
- ▶ **Acute Depression Randomized Care Pathway (RAD)** is a Sequential Multiple Assignment Randomized Trial (SMART) in STEP-BD
 - ▷ RAD was constructed to examine response to initial antidepressant treatments and secondary interventions for non-responders
 - ▷ **Antidepressant medication:** bupropion(wellbutrin), paroxetine(paxil)
 - ▷ Data analysis based on RAD present some evidence that subjects with a prior (hypo)mania episodes may not benefit from an adjuvant antidepressant [Wu et al., 2015]
- ▶ Standardized Care Pathway (SCP) is an observational study in STEP-BD
- ▶ **Standard Acute Depression Data (SAD)** set is constructed from SCP in STEP-BD
 - ▷ Patients in SAD satisfy RAD pathway entering criteria
 - ▷ **10** different **antidepressant medications**

SAD Data Structure

- ▶ Observe (X, A, Y) for each patient
 - ▷ X : Patient information prior to treatment assignment
 - ▷ A : Assigned treatment
 - ▷ Y : Overall depression score ($SUMD$) measured every 6-8 weeks
- ▶ $a \in \mathcal{A}$ has the form (t_1, d_1, t_2, d_2) :
 - ▷ t_j : Treatment from \mathcal{T}_j
 - ▷ d_j : Dose level at $t_j, d_j = 1, 2, 3$
 - ▷ $j = 1, 2$ two treatments for patients
- ▶ Treatments partitioned into groups: $\mathcal{T}_j = \bigcup_{k=1}^{\mu_j} \mathcal{G}_{kj}$ (see Table 1 and 2)
- ▶ SAD is an observational study (treatments not randomly assigned)



Optimal Treatment Regime for SAD

- ▶ Personalized medicine
 - ▷ Treatment given only if, when, and to whom it is needed
 - ▷ Better outcome less side effect
- ▶ A **treatment regime** $\pi : X \rightarrow A$ maps patient information X to a recommended treatment $\pi(X)$
- ▶ The optimal treatment regime minimizes mean outcome $SUMD$ when applied to population of interest
 - ▷ Estimate the optimal treatment regime using **grouped Q-learning**
- ▶ Data issues for SAD:
 - ▷ There is a significant amount of missing covariate information at both stages, **Multiple Imputation** is used to impute missing values
 - ▷ Variables are selected for grouped Q-learning model construction by **forward variable selection**
- ▶ **Antidepressants** are divided into **4** groups

Group Number	Medication Names
A1	Deseryl, Serzone
A2	Citalopram, Escitalopram Oxalate, Prozac, Fluvoxamine, Paroxetine, Zoloft
A3	Venlafaxine
A4	Bupropion

Table 1

- ▷ The dosage is divided into 3 levels: high, medium, low
- ▶ **Mood Stabilizers** are divided into **5** groups

Group Number	Medication Names
M1	Tegertol, Valproate
M2	Olanzapine, Quetiapine
M3	Clozapine
M4	Lithium
M5	Risperdal, Geodon, Abilify

Table 2

- ▷ The dosage is divided into 3 levels: high, medium, low
- ▶ Variable chosen for grouped Q-learning via variable selection is:
 - ▷ $SUMD_0$: overall depression score at baseline (0 - 16)
 - ▷ $MEDINS$: indicator of medical insurance (0: no, 1: yes)
 - ▷ $RACE$: indicator of race (0: others, 1: white)

SAD Analysis Result

- ▶ Estimated optimal regime with $RACE = 1, MEDINS = 1$:

$SUMD_0$	Optimal Treatment
[0, 6)	Low M2, Medium A2
[6, 8)	Low M2, High A1
[8, 10)	High M1, High A1
[10, 12)	Medium M1, Medium A2
[12, 14)	Medium M1, Low A2
[14, 16]	Medium M2, High A3

- ▶ Estimated optimal regime with $RACE = 1, MEDINS = 0$:

$SUMD_0$	Optimal Treatment
[0, 8)	Low M2, Medium A2
[8, 10)	Low M2, High A1
[10, 12)	Medium M1, Low A2
[12, 16]	Medium M2, Low A2

- ▶ Estimated optimal regime with $RACE = 0, MEDINS = 1$:

$SUMD_0$	Optimal Treatment
[0, 6)	Low M2, Medium A2
[6, 8)	Low M2, High A1
[8, 10)	High M2, Medium A2
[10, 16]	High M2, High A3

- ▶ Estimated optimal regime with $RACE = 0, MEDINS = 0$:

$SUMD_0$	Optimal Treatment
[0, 8)	Low M2, Medium A2
[8, 16]	High M2, High A3

- ▶ Where
 - ▷ $M_i A_j$: group i mood stabilizer, group j antidepressant
 - ▷ Low, Medium, High: mood stabilizer or antidepressant dosage level

Conclusions and Future Work

- ▶ Grouped Q-learning give advice to the choice of medication and dosage
- ▶ Patients with more severe baseline depression in general require higher dose for $Race = 0$
- ▶ Try to connect optimal regime also with evolving patient's characteristics