

# Switch Rates during Acute Treatment for Bipolar II Depression with Lithium, Sertraline, or the Two Combined: A Randomized Double-Blind Comparison

## BACKGROUND:

- Bipolar II disorder is distinguished from Bipolar I due to patients spending more time in the depressed phase than in the hypomanic phase.
- Current recommendations for Bipolar II disorder include a mood stabilizer as a monotherapy; however current practice involves the potential addition of an antidepressant.
- The use of selective serotonin reuptake inhibitors (SSRIs) in a Bipolar I patients is contraindicated due to increased risk of mania. SSRI monotherapy has yet to be studied in Bipolar II patients to determine if increased risk of hypomania exists.

## OBJECTIVE

- To determine whether the use of SSRI monotherapy in Bipolar II patients increases the frequency of switching to hypomanic states; to assess the safety and treatment response rates for SSRI monotherapy, a mood stabilizer monotherapy, and a combination of both.

## METHODS

- **Design:** Randomized, double-blind, parallel, multicenter, controlled experimental study; Duration: 16 weeks
- **Inclusion criteria:** 18-65 years of age who met DSM-IV criteria for bipolar II disorder, were in a current major depressive episode, had a score of  $\geq 22$  (moderate or greater severity) on the Inventory of Depressive Symptomatology-Clinician Rated (IDS-C) scale, a score of  $\leq 8$  on the Young Mania Rating Scale (YMRS), a score of  $\geq 3$  on the depression severity subscale of the Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP) and a mania severity subscale score of 1 (not ill) on the CGI-BP
- **Exclusion criteria:** Mixed symptoms or psychosis, suicidality, a substance use disorder within the previous 3 months, a past history of nonresponse to lithium or sertraline for depression with  $\geq 6$  weeks of treatment at an adequate dosage
- **Primary outcome measure:** Frequency of switching to hypomanic state as defined by the Young Mania Rating Scale (YMRS) and the Clinical Global Impression for Bipolar Disorder (CGI-BP) scale, or mania as defined by the DSM-IV and confirmed by the Structured Clinical Interview for DSM-IV (SCID).
- **Secondary outcome measures:** Treatment response as defined by the Inventory of Depressive Symptomatology (IDS-C) scale, or the CGI-BP scale, incidence of treatment-emergent side effects, and dropout rate
- 142 patients were randomized to receive either:
  - Lithium at a minimum goal of 900 mg/day, titrated to therapeutic response  
OR
  - Sertraline at a minimum goal of 100 mg/day, titrated to response  
OR
  - Lithium + sertraline at their respective minimum doses, titrated to response
- Power of 80% with an alpha level of 0.05 to detect large differences in switch rates based on a sample size of 142 with an expected 50% dropout rate
- Data handling method was intent-to-treat

## RESULTS

- 62 patients completed the study: 22 in the lithium group, 26 in the sertraline group, and 14 in the combination group

- **Primary outcome measure:** An estimated 14% of participants experienced a switch to a hypomanic state; there was an estimated switch rate of 19.4% in the lithium group, 19.9% in the sertraline group, and 13.4% in the combination group after accounting for early study discontinuation. The difference was not statistically significant ( $p=0.784$ ). 75% of switches occurred in the first 5 weeks of treatment
- **Secondary outcome measures:** 62.7% of participants met treatment response criteria during the study period. The monotherapy groups exhibited a greater incidence of response than the combination therapy group, however this was not significant ( $p=0.093$ ). Patients in the combination therapy group had a significantly greater dropout rate of 34 (compared to 27 and 19) ( $p=0.031$ ). The difference in treatment-emergent side effects was not statistically significant.
- **Author's conclusion:** Lithium monotherapy, sertraline monotherapy, and lithium/sertraline combination therapy is associated with equivalent switch rates. Also, monotherapy is associated with less treatment discontinuation than combination therapy.

#### STRENGTHS

- Trial setup and dosing was appropriate
- Limitations to study were addressed
- Medications were appropriate given current recommendations

#### LIMITATIONS

- No method of adherence monitoring discussed
- Lithium levels frequently not found to be within target therapeutic range
- Potentially inadequate duration of study
- Data handling method inappropriate due to large dropout rate
- No data provided to indicate when dropouts occurred
- Power of 80% not met
- Most of the participants endorsed a history substance abuse which correlated with an increased incidence of switching. This makes the results less generalizable to a population who does not endorse a history of substance abuse.
- Failure to allow all medications to reach full effects before comparing efficacy

#### CONCLUSION

- Although the study showed that switch rates were not increased with SSRI monotherapy, the study had many limitations that restrict the validity of the results.
- Despite the limitations, it appears safe to consider SSRI monotherapy as a later-line option in patients who can not tolerate a mood stabilizer or combination therapy.
- Future research would be beneficial with a larger sample size, longer duration, and therapeutic lithium levels.

**Reference:** Altshuler L, Sugar C, McElroy S, Calimlim B, Gitlin M, Keck P, et al. Switch rates during acute treatment for Bipolar II depression with lithium, sertraline, or the two combined: a randomized double-blind comparison. *Am J Psychiatry*. 2017;174(3):266-276.