Conventional antidepressant pharmacotherapy has not been robustly effective for treatment of bipolar depression (BD). For example, no difference was found between patients with BD depression when randomized to treatment with a mood stabilizer plus either an adjunctive antidepressant or placebo. New medication classes are thus needed. Given emerging evidence for immune dysregulation in mood disorders, the aim of the study was to evaluate the antidepressant efficacy in bipolar depression of minocycline, a drug with neuroprotective and immune-modulating properties, and of aspirin, at doses selected to selectively inhibit cyclooxygenase 1 (COX-1).

**METHODS**

**EXCLUSION CRITERIA**
- Male or female outpatient between 18 & 65
- Meets DSM-IV-TR criteria for BD (type I, II or NOS)
- Current moderate to severe depressive episode
- Current depressive episode lasted for at least previous 4 weeks
- Score > 10 on QIDS-C-16

**STATISTICAL ANALYSIS**

Individual subject data was plotted to browse data trend. There was decreasing trend in MADRS for all drug conditions and there was no evidence of a site by study interaction (KU, LIBR, OU).

Next, a linear mixed-effect model (LMM) was tested with MADRS changes as dependent variable and with various combinations of independent variables. The tested independent variables were: visit or log-visit, Minon(−), ASAm(−), and 2- and 3-way interactions between these variables, and age, sex, BMI covariates. Random effect was modeled for the visit and intercept variables for each subjects or for each location and subjects hierarchically. Nearly 150 models of all possible combinations were tested and the best AIC model, which fitted best to the data with least number of variables, was searched.

The best (minimum AIC) model was:

\[
\text{madrs\_score_diffV1 = logVisit + Mino + ASA + logVisit: Mino + logVisit:ASA + Mino + ASA + logVisit:Mino + ASA + sex + random effect = } \sim \logVisit + 1 \text{ subject}
\]

In this model, MADRS change from visit 1 was fitted by logVisit, ASA, Mino, and 2- and 3-way interactions of these variables. Only sex covariate contributed to better fit, so age and BMI covariates were excluded. Random model effect of location did not contribute to better fit.

Statistics of the LMM analysis are shown in Figure 2 for madrs\_score\_diffV1\_bestAIC.txt.

Significant effects were seen for the main effect of logVisit (p<0.0001) and ASA (p=0.033) indicating that MDRS score decreased with more visits and ASA group (M+A, and P+A) showed larger decrease on average across visits, but no interaction of Visit: ASA.

To visualize this trend, Figure 2 shows the changes in MADRS compared to the first visit for ASA (M+A, P+A) and ASA (M+P, P+P) groups. Bar graph shows group averages and standard error of means for each visit. As seen in the figure, both groups showed decrease of MDRS as more visits with larger decrease of ASA+group for visit 2 through visit 5.

Same analysis was done for HAM-A and YMRS but no statistically significant effect of drug was found.

**EXCLUSION CRITERIA**
- Substance dependence within the last 1 year (except nicotine)
- Daily alcoholic beverage consumption >3oz of alcohol
- Known allergies or hypersensitivities, including asthmatic reaction, to: Tetracycline antibiotics, Aspirin, Other NSAIDS
- Current use of drugs that could increase the risks associated with minocycline or aspirin administration, like: Other NSAIDS, Other antibiotics, Anticoagulants, Acetazolamide, Methotrexate
- Known HIV, viral hepatitis or other chronic infection
- Pregnant or nursing women
- Woman attempting to conceive

**Table 1:** shows the demographics and severity scores for the four groups. Note: A blinded interim analysis led to dropping the ASA + Pl and Mino + Pl at the midpoint in recruitment to increase enrollment in the two remaining groups.

**BACKGROUND**

**INCLUSION CRITERIA**
- Male or female outpatient between 18 & 65
- Meets DSM-IV-TR criteria for BD (type I, II or NOS)
- Current moderate to severe depressive episode
- Current depressive episode lasted for at least previous 4 weeks
- Score > 10 on QIDS-C-16

**Figure 1:** Study Design

**CONCLUSION**

A statistically significant effect for ASA up through visit 5 and then a statistically significant effect for visits with placebo rising as the study went on such that the ASA effect while numerically higher was not statistically significant at the last visit (#7).

There was no benefit from the addition of minocycline to aspirin (M+A) compared to placebo to aspirin (P+A) overall but there was a suggestion for additive benefit in some subgroup exploratory analyses (i.e., participants with BMI > 30 and female participants). The bioassays may shed additional light on subgroup benefits as well as potential markers of response and/or prediction of response.

**DISCLOSURE**

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