Title

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Journal

Schizophrenia bulletin, 43(Suppl 1)

ISSN

1787-9965

Authors

Cadenhead, Kristin
Addington, Jean
Cannon, Tyrone
et al.

Publication Date

2017-03-01

Peer reviewed

$P = .055$, log rank test), while in the stratum with high depressive symptoms, transition to psychosis rates were 13% and 10% for groups with and without AD use, respectively ($\chi^2 = .226$, $P = .635$, log rank test). Furthermore, repeated measures analysis indicated that MADRS depressive symptoms significantly improved between baseline and 12-month follow-up in groups with and without AD use in both strata of severity of depressive symptoms (all $P < .001$). Repeated measures analyses for the other secondary outcomes also showed no significant clinical advantage for AD use compared to no AD use in groups with either high or low depressive symptoms.

Conclusion: This is the first analysis on the effects of ADs in a large cohort of UHR individuals. No statistically significant effects of ADs on outcomes were observed. The findings are limited by fact that ADs were provided as concomitant medication upon clinical discretion.

23. OMEGA-3 FATTY ACID VERSUS PLACEBO IN A CLINICAL HIGH-RISK SAMPLE FROM THE NORTH AMERICAN PRODROME LONGITUDINAL STUDIES (NAPLS) CONSORTIUM

Kristin Cadenhead*[,1], Jean Addington[2], Tyrone Cannon[3], Barbara Cornblatt[4], Daniel Mathalon[5], Tom McGlashan[3], Diana Perkins[6], Larry J. Seidman[7], Ming Tsuang[1], Elaine Walker[8], and Scott Woods[3]

[1]University of California, San Diego; [2]University of Calgary; [3]Yale University; [4]Zucker Hillside Hospital; [5]University of California San Francisco; [6]University of North Carolina; [7]Massachusetts Mental Health Center, Beth Israel Deaconess Medical Center, Harvard Medical School; [8]Emory University

Background: Omega-3 Fatty Acids (FAs), EPA (eicosapentaenoic acid) and DHA (Docosahexaenoic acid), are essential for normal brain development and may also have neuroprotective properties. Dietary supplementation of EPA and DHA has beneficial effects in medical illnesses as well as depression, bipolar disorder, and dementia. Abnormal FA metabolism may play a role in the etiology of psychiatric illness. Studies of erythrocytes and skin fibroblasts have shown reduced levels of FAs and phospholipids in schizophrenia.

Studies of Omega-3FA supplementation in schizophrenia have been mixed. Amminger et al performed a randomized, double-blind, placebo-controlled trial in 81 subjects with prodromal symptoms of psychosis. The treatment consisted of 1.2g/day of Omega-3FAs (700 mg EPA, 480 mg DHA). After 12 weeks, 2 (4.9%) of 41 individuals in the Omega-3FA group and 11 of 40 (27.5%) in the placebo group converted to a psychotic disorder. Omega-3FAs also significantly reduced symptoms and improved functioning.

The Aims of the current study were to replicate the Amminger study in Clinical High Risk (CHR) subjects from the NAPLS consortium.

Methods: This was a 24-week, randomized, double-blind, placebo, fixed dose-controlled study of Omega-3FA versus placebo in 127 CHR subjects. The Omega-3FA compound contained a 2:1 proportion of EPA to DHA. The total dose was 740 mg of EPA and 400 mg of DHA. Baseline diet characterization was assessed using a systematic checklist that includes Omega-3FA foods. In addition, fasting erythrocyte FA composition was assessed.

Results: Of the 127 CHR subjects recruited into the trial, 118 completed baseline assessment, and 70 (59%) completed the 6-month trial. Seven (10% Kaplan-Meier) subjects converted to psychosis during the 24 months. The rate of psychotic conversion did not differ in the Omega-3FA (13%) versus Placebo (8%) samples. Conversion to psychosis was predicted by low Omega-3FA rich foods in the diet (Wald Statistic = 4.96, $P < .05$). Although there were significant improvements in symptom and functioning over time in Mixed Model analyses, there were no significant group or Group × Time interaction effects.

Conclusion: The rate of conversion to psychosis in the present sample was lower than is typically observed in an at-risk population. Given the study attrition and low rate of conversion to psychosis, the trial was underpowered to replicate the conversion effect in the Amminger et al.'s study. Despite the overall improvement in symptoms and functioning over time in all subjects, there was no clear evidence of a differential effect in the sample on Omega-3FA vs Placebo. Further work is needed to better tease out the role of diet and Omega-3FA in mental illness. The finding of a significant association between baseline diet low in Omega-3FA rich foods and later conversion to psychosis raises the question of whether it is possible to influence both physical and mental health with lifestyle choices including diet.

24. THE CLINICAL DEVELOPMENT OF LUMATEPERONE (ITI-007) FOR THE TREATMENT OF SCHIZOPHRENIA

Kimberly Vanover[1], Christoph Correll[2], Alex Dmitrienko[3], Steve Glass[1], Cedric O'Gorman*[,1], Jelena Saillard[1], Michal Weingart[1], Sharon Mates[1], and Robert Davis[1]

[1]Intra-Cellular Therapies, Inc; [2]The Zucker Hillside Hospital; [3]Mediana Inc.

Background: Schizophrenia affects about 1% of the population and exerts a great burden on patients and caregivers. Newer treatments are needed to provide broad symptom control and improved tolerability. Lumateperone is an investigational agent in late-stage development for schizophrenia, bipolar depression and agitation associated with dementia. Through synergistic actions via serotonergic, dopaminergic and glutamatergic systems, lumateperone represents a novel therapeutic approach.

Methods: The late-stage schizophrenia program comprised three well-controlled trials in patients during an acute exacerbation. ITI-007-005 included 335 patients randomized to receive either lumateperone (60 mg or 120 mg), risperidone (positive control) or placebo for 4 weeks.

ITI-007-301 included 450 patients randomized to receive either lumateperone (60 mg or 40 mg) or placebo for 4 weeks. ITI-007-302 included 696 patients randomized to receive either lumateperone (60 mg or 20 mg), risperidone (positive control) or placebo for 6 weeks. The primary efficacy end point in all studies was PANSS total score change from baseline versus placebo.

Results: In studies ITI-007-005 and ITI-007-301, lumateperone 60 mg met the primary end point and demonstrated efficacy with statistically significant superiority over placebo at Day 28. Lumateperone 60 mg, which requires no dose titration, also showed early efficacy (week 1) on both the PANSS total score and the PANSS Positive Symptom subscale score in ITI-007-301, and maintained efficacy throughout the study. In ITI-007-301, lumateperone 60 mg also met the key secondary endpoint of statistically significant improvement on the CGI-S. In this study, lumateperone 40 mg separated significantly from placebo on the PANSS positive subscale and the CGI-S, but not on the primary endpoint. Pro-social benefits were also observed with lumateperone in both studies.

In ITI-007-302, neither dose of lumateperone separated from placebo on the primary endpoint in the pre-defined patient population. Risperidone did separate from placebo. While the same magnitude and trajectory of improvement with lumateperone 60 mg was observed in all 3 studies (005, 301 and 302), an unusually high placebo response was observed in this last study. Post-hoc analyses revealed improved treatment effects for lumateperone when placebo response was controlled for.

Across all studies, lumateperone was well tolerated and exhibited a safety profile similar to placebo. In 2 studies that included risperidone as an active control, lumateperone demonstrated statistically significant advantages over risperidone on key safety and tolerability parameters.

Conclusion: Lumateperone represents a new approach to the treatment of schizophrenia with unique pharmacology and a differentiating clinical profile.