antidepressant). Results from the two parallel investigations illustrate that antidepressant learning may be associated with positive symptoms in schizophrenia such as delusions, and also with impairments in executive function, such as set formation and shifting. These deficits are sensitive to pharmacological modification by both ketamine and modafinil. To explain these data, one hypothesis links positive symptoms to aberrant learning mechanisms within sub-cortical circuitry that impacts at the cortical level, and cognitive impairments to additional deficits in related cortico-striatal networks at the cortical level. The availability of longitudinal data for the id/e test in a large sample of first episode cases also enables investigation of the contribution of basic deficits at the initial simple discrimination learning phase to the executive impairments in set-shifting, (as well as test-retest reliability of such deficits), over the course of the disorder.

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LESSONS LEARNED FROM THE IMPLEMENTATION OF A CLINICAL TRIAL USING THE MATRICS-FDA-NIMH GUIDANCE

W. Rein and N. Peters
Sanofi-Aventis Research and Development, Malvern, PA, USA

Sanofi-Aventis is currently conducting a large (~700 patients), multi-site (~70), multi-country (US and Canada) study in patients with cognitive impairment diagnosed with schizophrenia, the CONNECT study. We have experienced both opportunities and challenges using the study methodology for this novel therapeutic approach. The study is a 24-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled trial to evaluate the efficacy and safety of three oral doses of AVE1625, a CB1-receptor antagonist, and placebo on top of an established treatment of either olanzapine, risperidone, paliperidone, quetiapine or aripiprazole monotherapy. The primary endpoint is the MATRICS Consensus Cognitive Battery; the co-primary endpoint for functional capacity is the UCSD Performance-Based Skills Assessment. 2. S-a acknowledges the many positive opportunities this experience has provided our company, both scientifically and professionally. These opportunities include guidance from the FDA regarding requirements for trial design and endpoints, expertise in the use of the MCCB and UPSA2 and the establishment of relationships with many experts in this therapeutic area. S-a’s involvement in the MATRICS-CT Scientific Board as a pharmaceutical partner has also been a unique and rewarding experience. Challenges occurred in the following areas: limited numbers of countries in which to perform the study, protocol design, need for increased financial resources and patient retention. The following actions are part of the lessons learned: Increase the number of sites and length of enrollment, use shorter treatment period, consider inclusion of schizoaffective diagnosis, include use of all SGAs, allow some form of combination antipsychotic therapy, reconsider age limit of diagnosis, use abbreviated assessments such as the UPSA Brief, consider all English speaking countries from the beginning (in the absence of translations), plan for 2 day visits for ‘heavy’ assessments weeks and consider using an inpatient setting if patients are there only for lack of outpatient placement. In conclusion, sanofi-aventis sees this as a positive endeavor that has provided the company with many ‘Lessons Learned’ which will be beneficial in future clinical trials. Additionally, the translations of the MCCB and development of the co primary functional outcome measures will be of importance for the upcoming studies. The company also recognizes the many experts who have helped us along the way.

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THE mGluR5 POSITIVE ALLOSTERIC MODULATOR, CDPPB, HAS ANTIPSYCHOTIC EFFECTS, IMPROVES MEMORY, AND INCREASES HEDONIA: RELEVANCE TO SCHIZOPHRENIA

Jason Martin Uslaner, N. O. Surles, J. D. Vardigan, S. L. Huszar, P. H. Hutson
Schizophrenia, Merck, West Point, PA, USA

Schizophrenia is marked by a cluster of behavioral and psychological deficits, generally classified into 3 subgroups: positive symptoms, negative symptoms, and cognitive deficits. Unfortunately, no currently prescribed medication effectively improves all of these symptom domains. Because accumulating evidence suggests that NMDA receptor hypofunction underlies at least some of the behavioral manifestations of schizophrenia and mGluR5 receptor activation is thought to positively regulate NMDA receptor function, we examined the influence an mGluR5 positive allosteric modulator (PAM), CDPPB, on behavioral assays relevant to schizophrenia. CDPPB (30 mg/kg ip) attenuated both amphetamine (1.5 mg/kg sc) and MK-801 (0.23 mg/kg sc) induced psychomotor activity, assays sensitive to compounds with antipsychotic potential. Furthermore, CDPPB (3 and 10 mpk ip) reversed an MK-801 (0.3 mg/kg ip) induced deficit in novel object recognition and passive avoidance learning, indicating that mGluR5 PAMs have pro-cognitive effects. Finally, we report that CDPPB (3 mpk ip) alleviated an MK-801 (0.3 mg/kg ip) induced deficit in hedonic valuation, a core feature of negative symptoms, as measured by the sucrose preference test. These results suggested that mGluR5 PAMs may have a novel therapeutic profile in that they might improve all of the symptom domains present in schizophrenia.

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