Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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participants to the risks associated with the investigational intervention. This is important in the testing of novel interventions in people. People with schizophrenia are also considered to be a vulnerable patient population. Benefit-risk analyses must take into account relevant vulnerabilities (including cognitive and social harm) that create unique risks, as well as the potential for research participants to benefit. If there are scientifically sound methodological reasons to use a placebo control and the risks are reasonable, then it is ethical to for consent. Consent must be valid, which is also an issue in people with schizophrenia. Research participants must be fully informed of alternative available treatment options; the probability they could be randomized to a placebo arm; the consequences of delaying treatment; the risks and benefits associated with the trial; the options to receive treatment if symptoms worsen; and the right to withdraw from the study. Competent research participants are capable of assessing the relative merits and risks of a trial. Denying research participants the option to evaluate a trial and consent to participate is overly paternalistic and a violation of their autonomy. Decisions on whether a vulnerable person or population should be included or excluded from a placebo-controlled trial should be made on a case-by-case basis.

ETHICS OF PLACEBO USE IN SCHIZOPHRENIA TRIALS

Paul S. Appelbaum
Columbia University

The ethics of placebo use in schizophrenia research has been a matter of contention for several decades. Opponents of placebo use once relied on the Declaration of Helsinki, which formerly required that “[i]n any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method”

However, the Declaration now admits the possibility of using placebos, at least in studies in which “no current proven intervention exists; or where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm.” This formulation suggests that two elements are critical to the ethical use of placebos: standard medications may not be effective with the population under study; the condition being studied is susceptible to substantial fluctuation in severity or to spontaneous remission; the measurement techniques being used in the study are unavoidably imprecise; substantial reduction of risk of exposure to experimental interventions is possible with placebo use; or substantial benefits are likely as a result of more rapidly determining whether the experimental intervention is effective. Minimization of risk can involve: selection of subjects who are less likely to be adversely affected by placebo; minimizing the number of subjects receiving placebo and the duration of its use; making available other forms of treatment during the study that have the potential to mitigate adverse consequences; and having procedures in place for close monitoring of subjects and prompt restoration of active treatment. To insure meaningful consent, investigators may want to screen potential subjects for decisional capacity, use multiple approaches to communicating information, emphasize the potential consequences of being off medication, and quiz potential subjects’ understanding of the study. Placebo use in schizophrenia studies requires clear justification and efforts to minimize harms, but using these approaches can be done in conformance with acceptable ethical standards.

PLACEBO CONTROLLED TRIALS IN PATIENTS SUFFERING FROM SCHIZOPHRENIA: METHODOLOGICAL ISSUES WITH AN INDIRECT EFFECT ON ETHICAL CONSIDERATIONS

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Placebo controlled randomized clinical trials continue to be required by regulatory authorities for the licensing of new drugs for schizophrenia and many experts also consider this methodology as the gold standard of evaluating antipsychotics. This is hotly debated in the field, mostly from an ethical perspective. Yet, there are a number of issues associated mostly with methodological challenges, which only indirectly impinge upon ethical concerns. These include feasibility, patient selection, attitudes and expectations, all of which have an impact on the generalizability of data acquired from placebo controlled clinical trials. Given that there is an increasing difficulty in convincing both patients and clinicians to participate in placebo controlled studies and taking into account high drop out rates in such studies, even in the active treatment arms, the concern has been raised that such data will not be informative for everyday clinical practice.

Symposium

THE LONG SEARCH FOR AN INFLAMMATORY COMPONENT IN SCHIZOPHRENIA

Chairpersons: Iris Sommer and Sabine Bahn
Discussant: Cynthia Shannon-Weickert

Sunday, 6 April 2014
4:15 PM – 6:15 PM

Overall Abstract: In the 19th century, Sigmund Freud already examined the blood of psychotic patients for the presence of infectious agents. At that time, it was the spirochette he searched for, as a sign of tertiary syphilis. Today, tertiary syphilis is rare, but psychiatrists still examine blood samples of patients with psychosis in search for inflammatory or infectious components to rule out Lyme Disease, for example, which can present with psychotic symptoms. The reason for their vigorous search is the importance of these components as an inflammatory or infectious cause that would have for the treatment of these patients. This symposium will provide an update on the long search for an inflammatory component in schizophrenia. We will present recent findings portraying a wide range of scientific approaches (ie proteomics, virology, cognition and RCTs) that investigate the immune hypothesis of schizophrenia. Bob Yolken will present findings from recent investigations on infectious agents in patients with schizophrenia. Faith Dickerson will present findings about the increased risk of schizophrenia associated with infectious and inflammatory markers including IgG antibodies to Toxoplasma gondii, IgG antibodies to gliadin, and C-reactive protein. The third speaker, Sabine Bahn, will provide an overview of recent findings from her lab on the expression of immunological and other protein analytes in peripheral blood, especially providing evidence of the existence of schizophrenia sub-groups. Bart van Berckel will present findings using the PK11195 tracer in PET studies, which identified increased activation of microglia cells in patients with schizophrenia, most pronounced in the medial temporal lobe. Finally, Iris Sommer will review the evidence from RCTs adding different types of anti-inflammatory components to antipsychotic treatment for patients with schizophrenia. All speakers provide evidence for an inflammatory, possibly an infectious cause, in patients with schizophrenia. This suggests that immune modulation could have beneficial effects for (some) patients with schizophrenia. Together, this symposium will provide an overview of the contemporary findings of infectious and inflammatory causes in schizophrenia and provide an update of the current literature on efficacy of anti-inflammatory drugs.

META-ANALYSES ON DOUBLE-BLIND RCTS ADDING DRUGS WITH ANTI-INFLAMMATORY PROPERTIES TO ANTIPSYCHOTIC MEDICATION

Iris Sommer1, Roos van Westrhenen, Marieke Bekemans, Lot de Witte, Stefan Leucht, René Kahn2

1Department of Psychiatry, University Medical Center, Utrecht, The Netherlands and Rudolf Magnus Institute of Neuroscience, Utrecht, The Netherlands; 2Brain Center Rudolf Magnus, Dept. Psychiatry, University Medical Center Utrecht

Background: The inflammatory hypothesis of schizophrenia is not new, but recently it has regained interest as more data suggest a role of the immune system in the pathogenesis of schizophrenia. If increased inflammation of the brain contributes to the symptoms of schizophrenia, reduction of the inflammatory status could improve the clinical picture. Lately, several trials have been conducted investigating the potential of anti-inflammatory
agents to improve symptoms of schizophrenia. This study provides an update regarding the efficacy of anti-inflammatory agents on schizophrenic symptoms in clinical studies performed so far.

**Results:** Our search yielded 26 double blind RCTs that provided information on the efficacy on symptom severity of the following components: aspirin, celecoxib, davaunetide, EPA/DHA fatty-acids, estrogens, minocycline and N-acetylcysteine (NAC). Of these components aspirin (mean weighted effect size (ES) 0.3, 95% CI 0.06-0.537, I2=0%), estrogens (ES 0.51, 95%CI 0.043-0.972, I2=69%) and NAC (0.45, 95% CI 0.112-0.779) showed significant effects. Celecoxib, minocycline, davaunetide and fatty acids showed no significant effect.

**Conclusion:** The results of aspirin addition to antipsychotic treatment seem promising, as does the addition of NAC and estrogens. These three agents are all very broadly active substances and it has to be investigated if the beneficial effects on symptom severity are indeed mediated by their anti-inflammatory aspects.

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**SERUM BIOMARKERS FOR PSYCHIATRIC DISORDERS**

Sabine Bahn1,2

1Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, UK; 2University of Rotterdam

**Objective:** Schizophrenia is a heterogeneous disorder traditionally diagnosed using DSM criteria, which do not necessarily reflect potential differences in underlying molecular phenotypes. I will present results exploring whether schizophrenia patients can be divided into subgroups with distinct molecular alterations in growth factors or immune molecules.

**Method:** Multiplexed immunoassays were used to measure 147 molecules in the serum of 180 acutely ill antipsychotic-naive schizophrenia patients and 350 controls. 50 of these molecules were related to growth factor and immune pathways and were selected for a hypothesis driven approach to identify subgroups within the schizophrenia cohort. This analysis aimed to evaluate whether each patient subgroup had specific abnormalities in molecules associated with the two molecules classes.

**Results:** Schizophrenia patients could be separated into two significantly distinct subgroups each of which demonstrated predominant molecular abnormalities in either growth factors or immune molecules. Immune molecules were largely increased whereas growth factor levels showed both increased and decreased levels in the respective patient subgroups. Findings were validated in an independent validation cohort.

**Conclusion:** This study suggests that abnormalities in growth factors and immune molecules, which have been associated reproducibly with the molecular manifestation of schizophrenia, do not coincide in the same group of patients. This may be of relevance for intervention studies that specifically target particular molecular mechanisms and could be a first step to deconstruct the complex schizophrenia syndrome based on molecular alterations.

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**THE MICROBIOME-THE MISSING LINK IN THE PATHOGENESIS OF SCHIZOPHRENIA**

Robert Yolken1, Faith Dickerson2

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Recent studies indicate that individuals with schizophrenia have evidence of immune activation that may contribute to disease pathogenesis. The source of this immune activation has not been identified but is likely to be related to both genetic and environmental components. Recently it has become apparent that the composition of microbes on mucosal surfaces, termed the microbiome, represents an important modulator of the immune response in humans and in experimental animals. The microbiome has been linked to the generation of an aberrant immune response and also been shown to modulate brain development and behavior in animal model systems. We employed high throughput sequencing to characterize the complete oro-pharyngeal microbiome of 41 individuals with schizophrenia and 32 controls without a psychiatric disorder. We also examined the role of probiotics in modulating the microbiome. Interim analysis indicates that there are large differences between case and control individuals in terms of bacterial, viral, and fungal composition. Individuals with schizophrenia had increased levels of lactic acid bacteria including Lactobacillus casei, Lactobacillus salivarius, Lactobacillus lactis, and Streptococcus thermophilus as well as several other species of streptococci including 5 mitis and 5 mutans. Several of these bacteria have been associated with altered TH2 immune responses, an immunological change also noted in schizophrenia. On the other hand individuals with schizophrenia had decreased levels of many non-pathogenic bacteria such as strains of Neisseria, Haemophilus, Prochlorococcus, and Shewanella. Within the group of individuals with schizophrenia, altered levels of microorganisms were associated with an increased prevalence of the deficit syndrome as well as increased levels of intestinal immune activation as indicated by antibodies to food and intestinal antigens. In terms of fungi, individuals with schizophrenia had higher levels of pathogenic yeasts such as Candida glabrata and Candida tropicalis, but lower levels of the relatively less pathogenic Candida albicans. We also characterized a number of known human viruses such as Herpesvirus and Papillomaviruses, as well as bacteriophages and novel viruses. The microbiome was significantly altered by probiotic therapy, with a tendency towards normalization following treatment. Furthermore, many of the species which are increased in the oral microbiome of individuals with schizophrenia, such as streptococci, are modifiable by the administration of antibiotic medications. These studies indicate that the oral microbiome is altered in individuals with schizophrenia and that the microbiome is a potential target for novel therapies.

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**INFECTIONS, INFLAMMATORY MARKERS AND SCHIZOPHRENIA**

 Faith Dickerson, R.H. Yolken

Sheppard Pratt from Johns Hopkins University, Baltimore, MD

**Background:** A number of markers of infectious and inflammatory diseases have been associated with schizophrenia. However previous investigations have not yielded definitive conclusions about the role of these agents in disease pathogenesis. Previous studies have been limited by the examination of single or small groups of agents within a single population.

**Methods:** In this study, we examine multiple antibodies to infectious agents and food antigens as well as protein markers of inflammation in well-characterized cohorts of individuals with established schizophrenia (those with a duration of illness at least two years, N=261), individuals with a recent onset of psychosis (within the previous two years, N=106), and non-psychiatric controls (N=233). Some individuals had markers evaluated at several time points and some markers were not measured in some individuals due to limited sample volumes. Linear regression methods were used to calculate the association between the markers in recent onset and in established schizophrenia patients in comparison with controls adjusting for demographic factors such as age, race, gender, and maternal education. Regression models were also adjusted for the performance of multiple measurements in samples obtained from the same individual at different time points.

**Results:** For the recent onset group, significant associations were found for IgG antibodies to measles (t=6.31, p<0.001); markers of intestinal inflammation, glialin (t=5.90, p<0.001) and bovine casein (t=4.74, p<0.001); human coronavirus (t=2.89, p=0.004); Toxoplasma gondii (t=2.20, p=0.029), and the group D retroviruses, Mason-Pfizer monkey virus (t=3.97, p<0.001) and murine leukemia virus (t=3.27, p<0.001). For the established schizophrenia group, significant associations were found for a general marker of inflammation, C-reactive protein (t=7.47, p<0.001); IgG antibodies to wheat gliadin (t=2.58, p=0.010) and another marker of intestinal inflammation, Saccharomyces cerevisiae (t=2.78, p<0.006), measles (t=2.37, p=0.018), Herpes simplex virus type 2 (t=2.56, p=0.011), and human coronavirus (2.67 p<0.008). No significant case control differences were found in either group for IgG antibodies to cytomegalovirus, Epstein-Barr Virus, varicella-zoster virus, or influenza A or influenza B viruses. Case control differences were not found in the levels of antibodies to Herpes simplex virus type 1. However, antibodies to this virus were associated with lower