Metropolitan area (population = 750,000) are treated. The following variables were collected from extensive medical records review: demographic information, detailed hematological information, medication and other active medical diagnoses that could have contributed to the neutropenia, clozapine regimen and use of GCS-F and lithium.

Results: The mean age at clozapine introduction was 35,9 yrs (range 16–56). The mean observation period following the index neutropenia lasted 7.2 years (range 4 months -19,4). The mean delay between the index neutropenia and the re-challenge was 2.4 months. Five out of these 22 patients experienced additional neutropenias, and 3 of these 5 patients experienced more than one additional neutropenias, one undergoing a total of 11 neutropenias. At the end of the observation period, 17/22 patients were still on Clozapine; among the five patients in whom clozapine was stopped, three had died, one from a paralytic ileus that was deemed clozapine-related, and 2 from non-clozapine related causes. One stopped Clozapine for a non-hematological side-effect, and only one stopped due to neutropenia, i.e., after an eleventh neutropenia despite concomitant GCS-F use.

Discussion: This study adds to available evidence that a clozapine re-challenge or continuation following a neutropenia can be reasonably considered once potential risks and benefits have been carefully analyzed and then discussed with the patient and his/her family in order to make a shared decision. Furthermore, the present results raise the possibility that continuing clozapine with stringent hematological monitoring may be considered in some cases of neutropenia that do not reach the agranulocytosis threshold. These results also support that conclusion that conditions other than hematological ones (e.g., severe constipation) should be closely monitored and rigorously addressed in order to ensure the safety of Clozapine use.

O12.3. EFFECTS OF FINGOLIMOD, A POTENT ANTI-INFLAMMATORY AGENT, ON BRAIN STRUCTURE, FUNCTION, AND SYMPTOMS IN SCHIZOPHRENIA

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Background: New medications with novel targets are needed for schizophrenia. Several lines of evidence indicate that inflammatory processes including aberrant lymphocytic activity may be related to the pathophysiology of this illness. These data suggest that agents with anti-inflammatory actions, including modulation of lymphocytes and their inflammatory substrates, may prove to be efficacious for schizophrenia. Fingolimod is a powerful anti-inflammatory agent that is used in the treatment of relapsing multiple sclerosis. It is a sphingosine-1-phosphate (S1P) receptor modulator that decreases circulating lymphocytes through sequestration in lymph tissues. In addition, evidence suggest that it stimulates oligodendrocytes and may enhance white matter integrity. The purpose of this study was to assess the effects of fingolimod in schizophrenia.

Methods: Subjects with schizophrenia (N=40) were recruited through the Indiana University Psychotic Disorders Programs and randomized 1:1 in a double-blind, eight-week clinical trial of fingolimod 0.5 mg/day and placebo. Circulating total lymphocytes were determined and effects were assessed on symptoms (PANSS), cognition (BACS), plasma cytokines, white matter integrity (DTI) and cortical connectivity (resting fMRI).

Results: Results revealed a significant decrease in lymphocytes in subjects taking fingolimod versus placebo (treatment x time; $F = 61.2$, $p < 0.001$). Fingolimod treated subjects had a mean maximal drop in lymphocytes from baseline of 79.2% with all fingolimod treated subjects experiencing decrements greater than 60%. There was a trend toward higher mean skeletal fractional anisotropy (FA) post-treatment in the fingolimod group. Within the fingolmiod group, there were significant or trend-level correlations between FA increase and decrease in lymphocytes in the genu and body of the corpus collosum and the right superior longitudinal fasciculus. There were also significant group-by-visit interactions in connectivity of left prefrontal cortical (PFC) seeds with clusters in the cerebellum, driven by higher PFC-cerebellum connectivity following fingolimod treatment. There were no improvements (treatment x time) in PANSS total ($F = 0.66$, $p= 0.52$), any of the PANSS subscales, or BACS composite score ($F = 0.54$, $p = 0.44$). Serious side effects were not observed, and a full safety report will be provided.

Discussion: Fingolimod produced a strong anti-inflammatory response with substantial reductions in circulating lymphocytes in all treated subjects. Brain effects were observed. However, this response was not accompanied by improvements in symptoms or cognition. These data suggest that fingolimod's target of S1P modulation and robust anti-inflammatory warrant further investigation in schizophrenia.

O12.4. EFFECTS OF THE GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST EXENATIDE ON BONE STATUS IN OBESE, NON-DIABETIC, ANTIPSYCHOTIC-TREATED SCHIZOPHRENIA SPECTRUM PATIENTS

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Background: Low bone mineral density (BMD) may constitute an underestimated comorbidity in schizophrenia patients undergoing long-term antipsychotic treatment. Glucagon-like peptide 1 (GLP-1) receptor agonists are antidiabetic drugs, which may also affect bone turnover.

The current study comprises planned secondary analyses of the 'TAO study': Treatment of antipsychotic-associated obesity with a GLP-1 receptor agonist. The TAO study was an investigator-initiated, double-blind, randomized, placebo-controlled trial, investigating the effects of three months treatment with the GLP-1 receptor agonist exenatide 2 mg once-weekly in chronic obese, antipsychotic-treated patients with schizophrenia spectrum disorder.

Methods: First, we compared baseline bone turnover markers (BTMs) of 45 chronic, obese, antipsychotic-treated patients with the Danish Health2006 study cohort as reference population, and we calculated bone mineral density (BMD) T- and Z-scores.

Second, investigated effects of three months of GLP-1 receptor agonist exenatide 2 mg once-weekly (n=23), or placebo (n=22) on BTMs and BMD in these patients. Data were initially analyzed without covariates by two-way repeated measures ANOVA. All analyses were repeated with mean prolactin level as a covariate to evaluate the potential effect of prolactin.

Results: In women (n=24), all baseline BTM measurements of procollagen type I N-terminal propeptide (PINP) and C-terminal cross-linking telopeptide of type I collagen (CTX) were within reference values. In men (n=21), 5% displayed lower PINP and 14% displayed lower CTX. One patient displayed BMD Z-score <-2, and 23% of patients (17% of women and 29%