in schizophrenia patients as fewer and delayed relapses over the course of a lifetime of schizophrenia may provide higher protection against grey matter damage and help preserve functioning.

T46. TARGETING THE IMMUNE SYSTEM TO TREAT DEPRESSION AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Background: Negative symptoms consist of impaired quality of life, social isolation, reduced emotional responsiveness, self-neglect and anhedonia, which have been categorised into avolition-apathy and expressive deficits sub-domains. The treatment of negative symptoms remains a challenge. Depression is commonly seen in schizophrenia and previous findings have suggested a relationship between depression and negative symptoms via the avolition-apathy sub-domain, (Barnes et al., 2016). It is possible this is the result of a common aetiology, distinct from expressive deficit or other symptoms of schizophrenia. Immune dysfunction has been implicated in both psychotic and depressive illnesses; increased circulating pro-inflammatory markers (such as IL-6, TNF-α & CRP). This suggests a novel target for treatments. A putative neuroprotective role of minocycline has been suggested via reducing microglial activation, and decrease in the production of cytokines including IL-6. Minocycline has been shown to be effective in the treatment of negative symptoms (Xiang et al., 2017) and depression (Soczynska et al., 2012). Within schizophrenia, we predict that that minocycline will lead to a longitudinal improvement in depression and the avolition-apathy sub-domain of negative symptoms
Methods: Data from the BeneMin study will be presented. BeneMin recruited 207 patients with a current research diagnosis of schizophrenia within 5 years of onset and randomised to minocycline (300mg/day) or matching placebo for 12 months adjunctive to antipsychotic medication. For this analysis the primary outcome variable is the negative symptom subscale from the Positive and Negative Syndrome Scales (and broken down into avolition-apathy and expressive deficits sub-domains), Calgary Depression Scale in Schizophrenia (CDSS) and circulating IL-6, TNF-α and CRP over 4-time points 2, 6, 9, and 12 months.
Results: At baseline, 40% were depressed (mean CDSS score = 5). The mean avolition-apathy PANSS score was 9.5 and expressive deficits was 9, and was comparable across placebo and minocycline arms. Preliminary results show that markers of inflammation were low in both treatment arms, compared with previous research (baseline CRP Md = 1.45, IL-6 Md = .57, TNF-α Md = 2.43) and this was comparable across depressed and non-depressed patients. TNF-α was significantly associated with expressive-deficits (B = .75, p = .005). Conversely, no marker of inflammation was associated with avolition-apathy or depression. However, in four linear mixed effect models across the 2, 6, 9 and 12-month follow-up assessments compared with placebo, minocycline had no effect on total negative symptoms, avolition-apathy, expressive deficits or depression. Further analysis stratifying patients by depression scores and markers of inflammation will be presented.
Discussion: Preliminary results indicate that minocycline does not lead to a reduction in avolition-apathy or depression in early schizophrenia. This may be the result of a medicated, sample recruited within 5 years of illness onset, and low levels of depression. Future studies should target depression in psychosis as a primary aim with samples of individuals with increased inflammatory response to fully investigate minocycline's potential in targeted intervention.

T47. IS THERE A DIURNAL VARIATION IN PSYCHIATRIC SYMPTOMS IN SCHIZOPHRENIA?

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Background: Anecdotally we have observed subgroups of schizophrenic patients who experienced a diurnal variation in a wide range of psychiatric symptomology. Such a pattern could have substantial ramifications in both clinical care and clinical trials. For example, two commonly used measures of symptom severity in clinical trials, the Positive and Negative Symptom Scale (PANSS) and the Negative Symptom Assessment Scale (NSA-16) contain numerous items that are rated based entirely or in part on observations of the subject during the interview. We hypothesized that inconsistency in the time of day of assessment in subjects whose symptoms were influenced by circadian rhythms could introduce an erratic "noise" element in the longitudinal measure of their symptoms.
To investigate this hypothesis we compared the change in PANSS total score and individual PANSS items across consecutive visits by whether the assessments had been conducted at consistent vs. inconsistent times of day.
Methods: 2109 individual subject visits from multiple schizophrenia clinical trials for which PANSS interview start time was available were included in the analysis. 1,764 pairs of consecutive PANSS interviews within individual subjects were identified and the time difference between the start times of the interviews were calculated. The absolute time difference was divided into quartiles and the first quartile (assessments least disparate in time) and the fourth quartile (assessments most disparate in time) were compared in the analyses. The mean absolute change in PANSS total and PANSS individual items between the consecutive visits was compared between the 2 groups using a t-test. Given the exploratory and hypothesis driven nature of the analysis we did not correct for multiple comparisons.
Results: The average absolute difference in interview start times was 79.5 minutes. The group with assessments closest in time (N = 446) had their interviews start no later than 30 minutes apart while the group with assessments most disparate in time (N = 445) had their interview start with at least 170 minutes difference. Of the 30 PANSS items, items P4 (Excitement 0.33 vs. 0.44, p =0.0077), P7 (Hostility 0.31 vs. 0.47, p < 0.001), N5 (Difficulty in abstract thinking 0.28 vs. 0.35, p = 0.043), N7 (Stereotyped thinking0.26 vs. 0.35, p = 0.021) G1 (Somatic concern 0.34. vs. 0.43, p = 0.041), G2 (Anxiety 0.42 vs. 0.53, p = 0.019), G6 (Depression 0.38 vs.0.52, p = 0.0044), G7 (Motor retardation 0.28 vs. 0.37, p = 0.025), and G8 (Uncooperativeness 0.29 vs. 0.39, p = 0.02) had an absolute difference significantly higher in the disparate group than in the close group. The mean absolute difference in the PANSS total was 5.1(+/-5.8) in the close group and 5.9(+/-5.4) in the disparate group, (p = 0.08).
Discussion: The results demonstrate a statistically significant effect of variation in time of day on symptom severity. These findings underscore the risk of potential noise (erratic changes) in longitudinal assessment of symptom severity when ratings are done at different times of day. Moreover, it suggests that symptom severity assessed in a standard PANSS interview may not generalize over the entire day, much less over the standard one week rating period. This is important because many PANSS items are rated partially or entirely on the interview which may not be a representative "biopsy" of the subject's mental state or behavior during the one week rating period. This highlights the potential remedies of more frequent or ecological measurements.
Hufford et al (2014) demonstrated a statistically significant effect of variation in the time of day on signal from the MCCB cognitive battery. Our results confirm our anecdotal observations that severity of non-cognitive schizophrenic symptoms are impacted by circadian rhythms as well.