Background: Recent research in schizophrenia has revealed that there is no consensus to which is the most appropriate definition for antipsychotic response. Response rates allow the clinician to know how many subjects have responded to a specific treatment. However, once again, levels of response or the cutoff chosen have been subject of controversy, as a high variety of values have been applied in schizophrenia research. This systematic review aimed to examine all the definitions used for antipsychotic response in delusional disorder (DD), to analyze them and provide a discussion of the methodology used.
Methods: A systematic computerized literature search was performed by using Pubmed, Scopus and PsycINFO databases (1990-September 2017) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. In addition, reference searches were manually conducted through identified studies in order to obtain other relevant articles not previously found on the initial search strategy. The following search terms were used: [(Antipsychotic response) OR (antipsychotics) OR (treatment response)] AND [(delusional disorder)]. Studies were only included if the met our inclusion criteria: (a) be published in a peer-reviewed journal, (b) prospective or retrospective studies focusing on antipsychotic response, (c) studies assessing response in DD based on clinical judgment or clinical records, (d) studies including a definition of antipsychotic response based on assessment scales and (e) diagnostic criteria based on ICD or DSM. The literature search strategy was conducted independently by two of the authors (A.G. and F.E.). The last search was conducted on 30th October, 2017.
Results: Seventy-four studies were initially identified. 39 studies were excluded after titles and abstracts were read, as they did not meet our initial inclusion criteria or met any of the exclusion criteria. 22 studies were excluded after reading the full text-document as they failed to meet our inclusion criteria or met any exclusion criteria, and 2 articles were excluded as studies for the assessment were duplicated. After the screening and selection processes, a total of 11 studies met our inclusion criteria, using different methods to define antipsychotic response in DD. Chart review (n=5) and observer-rated scales (n=6), from which 2 of them used the CGI improvement scale for assessing response, 2 studies evaluated it by mean changes from baseline to endpoint scores (PANSS, BPRS), one study combined the CGI improvement scale and mean changes from baseline scores (PANSS), and one study reported responder rates based on a scale-derived cutoff (PANSS).
Discussion: A lack of consensus in the definitions of antipsychotic response in delusional disorder and a high degree of heterogeneity of the methods used are reflected on this systematic review. Although no consensus for the response definition appears to exist in delusional disorder, there is a need to better quantify the treatment response in terms of percentages of response, and linking these findings with those derived from the CGI. Recommendations from Leucht (2014) in schizophrenia would be a first step in defining response among delusional disorder patients.

T226. CLINICAL PREDICTORS OF FUNCTIONAL CAPACITY IN TREATMENT RESISTANT SCHIZOPHRENIA PATIENTS: COMPARISON WITH RESPONDER PATIENTS, ROLE OF NEGATIVE SYMPTOMS, PROBLEM SOLVING DYSFUNCTIONS, AND NEUROLOGICAL SOFT SIGNS

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Background: Treatment Resistant Schizophrenia (TRS) patients show more severe impairments in community functioning compared to Antipsychotic Responder Schizophrenia (ARS) patients. The scope of this work was to assess whether TRS patients suffer from more severe alterations in functional capacity, i.e. the baseline potential of a patient to function in the community, and whether factors affecting functional capacity differ between TRS and ARS patients.
Methods: 60 out of 182 eligible patients were included. A multistep diagnostic procedure to separate TRS from ARS was then used. Patients were administered a range of assessment tools including (but not limited to): the PANSS; cognitive performances tests; the Specific Level of Functioning (SLOF); the Neurological Evaluation Scale (NES); the UCSD Performance-Based Skills Assessment (UPSA) extended version. Univariate and multivariate statistics were performed. Significance was set at $p<.05$.
Results: After controlling for covariates, no significant differences in both total and subscales UPSA scores were found between TRS and ARS patients. However, TRS patients constantly scored lower than ARS patients. Stepwise regression was used to determine predictors of UPSA score. The first group encompassed clinical variables. In the whole sample, the final significant model, $F(2,57)=18.848$, $p<.0005$, adjusted $R2=.37$, included: PANSS negative subscale score and NES score. In TRS patients, the final significant model, $F(3,24)=16.552$, $p<.0005$, adjusted $R2=.63$, included PANSS negative scale score, education years, and NES score. In ARS patients, no significant models were found.
The second group included cognitive performance variables. In the whole sample, the final significant model, $F(2,57)=7.64$, $p=.001$, adjusted $R2=.18$, included Problem Solving and Verbal Memory. In TRS patients, the final significant model included Problem Solving and VisuoSpatial Memory. In ARS patients, the final significant model included Verbal Memory only.
The third group included psychosocial variables. In the whole sample, the final significant model, $F(1,58)=18.82$, $p<.0005$, adjusted $R2=.23$, included SLOF Area5 score only. In TRS patients the final significant model included SLOF Area1 score only, while in ARS patients, no significant models were found.
By hierarchical multiple regressions, NES score was found to be predictive of the highest UPSA score variance ratio among schizophrenia patients. The addition of PANSS Negative scale score and Problem Solving (in this order) led to a statistically significant increase in R2. No further models were found to add significant increase in R2. In TRS patients, PANSS Negative scale score was the variable that explained the most variance in UPSA score. The addition of Problem Solving and education years (in this order) led to a statistically significant increase in R2. No further models were found to add significant increase in R2, although NES score showed a trend toward significance.
At last, we performed a path analysis to evaluate the type (direct or indirect) and the direction of relationships among these variables and UPSA score. The only variables that were in direct relationship with UPSA score were PANSS Negative Scale score and Problem Solving. SLOF Area5 was in indirect relationship with UPSA score by PANSS Negative Scale score, while NES score relationship with UPSA score was mediated by Problem Solving.
Discussion: Our study demonstrated that negative symptoms, altered cognitive performances, and more severe neurological soft signs were the major factors influencing functional capacity in schizophrenia patients. These factors were more relevant in TRS than in ARS patients.

T227. THE METABOTROPIC GLUTAMATE RECEPTOR SUBTYPE 1 REGULATES STRIATAL DOPAMINE RELEASE VIA AN ENDOCANNABINOID-DEPENDENT MECHANISM: IMPLICATIONS FOR THE TREATMENT OF SCHIZOPHRENIA

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Background: Clinical and preclinical studies suggest that selective activators of the muscarinic M4 receptor have exciting potential as a novel approach for treatment of schizophrenia. M4 reduces striatal dopamine (DA) though release of endocannabinoids (eCB), providing a mechanism for local effects on DA signaling in the striatum. M4 signals through Gαi/o and does not couple to Gαq/11 or induce calcium (Ca++) mobilization. This raises the possibility that M4-induced eCB release and inhibition of DA release may require co-activation of another receptor that activates Gαq/11. If so, this receptor could provide a novel target that may be more proximal to inhibition of DA release. Interestingly, the group 1 metabotropic glutamate (mGlu) receptors (mGlu1 and Glu5), couple to Gαq/11 and activate eCB signaling in multiple brain regions.
Methods: We tested the hypothesis that M4-induced reductions in DA release and subsequent antipsychotic-effect requires co-activation of group 1 mGlu receptors. The effect of M4 activation on electrically-evoked DA release in striatal slices was assessed using fast-scan cyclic voltammetry (FSCV) in the absence or presence of selective negative allosteric modulators (NAMs) of group 1 mGlu receptor subtypes. To evaluate the potential role of mGlu1, we determined the effects of a selective mGlu1 positive allosteric modulators (PAMs) on striatal DA release and antipsychotic-like activity in rodent models that are dependent on increased DA transmission. Since reductions in DA signaling, including D1 signaling have been implicated in reduced motivation, we also determined the effects of an mGlu1 PAM, M4 PAM, and the typical antipsychotic haloperidol on motivational responding in a progressive ratio (PR) schedule.
Results: We now present exciting new data in which we found that activation of mGlu1 through application of exogenous agonists or selective stimulation of thalamostriatal afferents induces a reduction of striatal DA release and that selective mGlu1 PAMs have robust antipsychotic-like effects in rodent models. Interestingly, our studies also suggest that mGlu1 activation is required for M4 PAM-induced inhibition of DA release and antipsychotic-like effects. However, in contrast to available antipsychotic agents, the present results and previous studies suggest that mGlu1 and M4 PAMs reduce DA signaling through local release of an eCB from striatal SPNs and activation of CB2 receptors on neighboring DA terminals to reduce DA release. While these studies suggest that the effects of M4 PAMs on DA release require activation of mGlu1, we have also found that these targets have important differences. Most notably, M4 PAMs also directly inhibits D1 signaling in D1-SPN terminals in the substatnia nigra pars reticulata (SNr). Unlike M4, mGlu1 does not directly inhibit DA D1 receptor signaling and does not induce behavioral changes that could be associated with negative symptoms.
Discussion: Our findings are especially interesting in light of recent findings that multiple loss of function single nucleotide polymorphisms (SNPs) in the human gene encoding mGlu1 (GRM1) are associated with schizophrenia, and points to GRM1/mGlu1 as a gene within the "druggable genome" that could be targeted for treatment of schizophrenia. Recent clinical imaging studies suggesting that symptoms in schizophrenia patients are associated with selective increases in striatal DA signaling and while extrastriatal regions display hypo-dopaminergic function; thus, mGlu1 and M4 PAMs may provide a mechanism for selective inhibition of DA release in striatal regions that are important for antipsychotic efficacy, without further disruptions in extrastriatal DA signaling.

T228. VARIABILITY AND UNDERUTILISATION OF CLOZAPINE IN SPAIN

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Background: The analysis of the information available in many countries on the use of clozapine, systematically indicates low prescription, underdosing and delay in the start of treatment. But as striking as this underutilization is the great variability between territories studied, which are related to multiple factors, and have led to various initiatives to improve its use. We do not have studies that evaluate these aspects in the Spanish population, so we have considered a first approximation through samples from four territories.
Methods: The authors analyzed the prescription data of clozapine in Castilla y León, the Basque Country, Catalonia and a Southern Madrid Area.
Results: The patients diagnosed with schizophrenia who receive treatment in the territories studied oscillate around 0.3%; the treatments with clozapine / 10000 inhabitants between 33.0 and 57.0; and patients diagnosed as schizophrenia receiving clozapine account for between 13.7% and 17.9% of those treated. The coefficient of variation between centers and prescribers is frequently higher than 50%.
Discussion: The global clozapine prescription data in the territories studied are in the range of countries in our environment. The variability in the prescription is very high and increases as we analyze smaller territories, until a great heterogeneity of the individual prescription.

T229. ANTIPSYCHOTIC DRUG USE AND THYROID FUNCTION IN PATIENTS WITH SEVERE MENTAL DISORDERS

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Background: Altered levels of free Thyroxin (fT4) and Thyroid Stimulating Hormone (TSH) have been associated with severe mental disorders and the use of antipsychotic drugs. Still, there is a lack of studies systematically investigating commonly prescribed antipsychotic drugs and thyroid function. We investigated the association of antipsychotic drugs and thyroid hormones levels in patients with severe mental disorders and compared thyroid function tests between patients and healthy controls under real-life conditions.
Methods: We included 1345 patients with schizophrenia or bipolar disorders and 989 healthy controls from the on-going Thematically Organized Psychosis (TOP) study, recruiting participants between 18–65 years of age in and around Oslo, Norway. All patients underwent a thorough clinical investigation including diagnostic evaluation, somatic screening and assessment of medication data. Serum drug concentrations were measured. Plasma levels of fT4 and TSH were measured in patients and healthy controls, and thyroid status was determined based on the combined hormone levels. Participants with known thyroid function disorders (N=28) were excluded. Mann-Whitney U tests and chi-square tests were performed for comparison between groups. For evaluation of influence from antipsychotics, multiple linear regression analyses were performed, adjusting for patient/control status, age, sex and use of other psychopharmacological agents. Associations with the use of olanzapine, quetiapine, aripiprazole or risperidone in monotherapy were analyzed in a subsample of patients (N=480), adjusting for age, sex and diagnosis. Spearman correlation analyses were performed for hormone levels and drug serum concentrations.
Results: We found significant lower levels of fT4 (median 13.70 vs 14.00, $p<0.001$) and higher levels of TSH (median 1.92 vs 1.57, $p<0.001$) in patients compared to healthy controls. A significant difference between patients and controls in occurrence of hyper- and hypothyreosis was observed ($p<0.001$), with more than three times as many patients compared to controls with hypothyroid status (11.1% vs 3.4%), and a doubling of hyperthyroid status (2.3% vs. 1.2%). Use of antipsychotics was significantly