he undergoes during the psychotic experience. The subjective perception of change is a position that can easily lead to connect with painful and depressive feelings, so it can be assumed that subjective insight could be related more consistently with the depressive symptoms than the clinical insight.
Methods: Observational cross-sectional study of a group of 114 schizophrenia patients treated in the psychiatry devices of the Parc de Salut Mar and Parc Taulí Instruments: SUMD, Markova and Berrios Scale and Calgary scale for depression in psychosis.
Results: Subjective insight is significantly correlated with Lindenmayer's depressive factor and depression level measured by a Calgary scale.
Clinical insight correlates with positive and excitatory symptoms. The time of evolution explains the non-awareness of the social consequences of the disease.
Discussion: The subjective insight into schizophrenia is mainly related to the depressive symptoms. The clinical insight into schizophrenia is related to positive symptoms.

S219. RISK FACTORS FOR LOW BONE MINERAL DENSITY IN PATIENTS TAKING ANTIPSYCHOTICS

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Background: The aim of this study is to explore potentially modifiable risk factors for low bone mineral density (BMD) in adults with psychotic disorders. Furthermore, we sought to identify gender-specific risk factors.
Methods: The study included 285 community-dwelling patients with psychotic disorders. Dual-energy x-ray absorptiometry was used to measure BMD. Laboratory examinations included vitamin D and prolactin levels. Low BMD was defined as<1 standard deviation below the mean for young adults. Clinical characteristics associated with low BMD were identified with logistic regression analysis in total population and each gender.
Results: Fifty-eight (20.4%) subjects had low BMD. Low BMD was more common in men and in patients with low body mass indices (BMIs), as well as in those with shorter treatment durations, those on Medicaid, and patients using serotonergic antidepressants. Logistic regression analysis revealed that low BMD was negatively associated with BMI and treatment duration and positively with gender (male) and serotonergic antidepressants use in the overall population. In men, low BMD was associated with treatment duration and BMI; in women, low BMD was associated with BMI, prolactin level, vitamin D, and serotonergic antidepressant use.
Discussion: Low BMI was risk factor for reduced BMD in both genders. Shorter treatment duration was associated with low BMD in men, whereas higher prolactin levels, lower vitamin D, and the use of serotonergic antidepressants were associated with low BMD in women. Psychotropic agents should be prescribed mindful of their effects on bone, as use of these medications is a modifiable risk factor for osteoporosis in women with psychotic disorders.

S220. BLONANSERIN AUGMENTATION IN PATIENTS WITH SCHIZOPHRENIA – WHO IS BENEFITED FROM BLONANSERIN AUGMENTATION? AN OPEN-LABEL, PROSPECTIVE, MULTI-CENTER STUDY

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Background: Evidences for antipsychotic augmentation for schizophrenic patients with sub-optimal efficacy have been lacking although it has been widespread therapeutic strategy in clinical practice. The purpose of this study was to investigate the efficacy and tolerability of blonanserin augmentation with an atypical antipsychotics (AAPs) in schizophrenic patients.
Methods: A total of 100 patients with schizophrenia partially or completely unresponsive to treatment with an AAP recruited in this 12-week, open-label, non-comparative, multicenter study. Blonanserin was added to existing AAPs which were maintained during the study period. Efficacy was primarily evaluated using Positive and Negative Syndrome Scale (PANSS) at baseline, week 2, 4, 8, and 12. Predictors for PANSS response (≥20% reduction) was investigated.
Results: The PANSS total score was significantly decreased at 12 weeks after blonanserin augmentation (-21.0 ± 18.1, F=105.849, p<0.001). Response rate on PANSS at week 12 was 51.0%. Premature discontinuation was occurred in 17 patients (17.0%) and 4 patients among them discontinued the study due to adverse events. Nine patients experienced significant weight gain during the study. Response to blonanserin augmentation was associated with severe (PANSS>85) baseline symptom (OR=10.298, p=0.007) and higher dose (>600mg/day of chlorpromazine equivalent dose) of existing AAPs (OR=4.594, p=0.014).
Discussion: Blonanserin augmentation improved psychiatric symptoms of schizophrenic patients in cases of partial or non-responsive to an AAP treatment with favorable tolerability. Patients with severe symptom despite treatment with higher dose of AAP were benefited from this augmentation. These results suggested that blonanserin augmentation could be an effective strategy for specific patients with schizophrenia.

S221. QUANTITATIVE SYSTEMS PHARMACOLOGY AS AN ALTERNATIVE TO CHLORPROMAZINE EQUIVALENTS: PREDICTIVE VALIDATION FROM A CRIS DATABASE EXPERIMENT

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Background: Polypharmacy is common in real clinical practice and in pharma-sponsored clinical trials. Chlorpromazine equivalents do not take into account pharmacodynamic interactions of drug combinations. If there is a sufficiently deep calibration set available, bio-informatics approaches can build classifiers for clinical phenotypes. However, this is not always the case which severely limits the generalizability of the predictions.
Methods: We applied a mechanism-based computer model of a cortico-striatal-thalamocortical loop of the dorsal motor circuit that has been calibrated with clinical data on the prevalence of extrapyramidal symptoms after antipsychotic treatment in schizophrenia patients and therapeutic interventions in Parkinson's patients[1]. The Quantitative Systems Pharmacology (QSP) model is based on the appropriate connections between basal ganglia regions and consists of 220 neurons (8 different cell types), 3500 synapses and implementations of 32 CNS active targets, based on their unique locations and coupling with intracellular pathways. Modulation of the various CNS targets were calculated on simulating the competition between the endogenous neurotransmitter and the two drugs at their appropriate concentrations and affinity.

The model was challenged to blindly predict the extrapyramidal symptoms liability of 1,124 patients prescribed two antipsychotics for six or more months (772 unique combinations). Anonymized data were derived from South London and Maudsley NHS Foundation Trust (SLAM) electronic health records (EHR). Extrapyramidal side effects were captured and identified using a combination of Natural Language Processing and a bespoke algorithm [2]. Only names and doses of the two drugs were made available without any calibration set.

Results: Blind prediction of the outcomes using a Receiver Operating Characteristic curve with the QSP model resulted in an Area-Under-the Curve of 0.64 ($p<0.01$), compared to an AUC of 0.52 for the sum of the chlorpromazine equivalents, 0.53 for the sum of affinity constants or the sum of D2R occupancies of the individual antipsychotics (AUC=0.52).

Discussion: QSP is a powerful approach to predict PD-PD interactions in the absence of any calibration set or with limited and unique data and is superior to chlorpromazine equivalents for predicting EPS liability. A major application is the simulation of pharmacodynamic interactions of comedications in clinical trials with novel compounds leading to possible better balance between the different treatment arms

S222. CLINICAL UTILITY OF PHARMACOGENETIC TESTING IN SCHIZOPHRENIA TREATMENT

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Background: Antipsychotics (APs), antidepressants (ADs) and mood stabilizers are essential components in treatment of most psychiatric disorders and in particular in schizophrenia. Unfortunately, among the various compounds which have been developed, lengthy trials are often required before the optimum medication treatment is found, i.e. with most significant symptom alleviation and minimal side effects. Thus, predictive factors would thus be extremely beneficial in clinical practice. The underlying reasons for this large inter-individual
variability in terms of treatment response are not fully understood. Important factors that influence drug dose, response and side effects include age, gender, patient compliance, constellation of symptoms, co-morbidity, and to a large extent genetic factors.

Methods: Methods follow two strategic concepts, i.e. 1) review of the literature and review of the clinical utility of using genetic information preemptively and 2) results of own studies evaluating treatment outcome in psychiatric care after genetic information (e.g., CYP2D6 and CYP2C19) was provided to more than 350 physicians.

Results: There is growing consensus among expert that genetic testing to optimize medication treatment in psychiatry meets criteria for clinical utility. However, utility remains restricted to specific gene-drug pairs and multi-gene test require further validation.

Our own research has shown that variation in genes involved in the metabolism of psychotropic drugs (pharmacokinetics) and genes encoding drug targets, such as brain receptors (pharmacodynamics) are associated with plasma drug levels, treatment response, and side effects (e.g., antipsychotic-induced weight gain). In addition, our genome-wide analyses have revealed associations with clinical outcome to antipsychotics or antidepressants and markers in neurotrophins, cell-signaling and inflammatory pathways.

With respect to our preemptive genetic testing program in more than 10,000 patients, we received supportive responses from physicians who enrolled patients in our study. Notably, while the vast majority of patients reported improvement in patient outcome, only two physicians indicated that their patient's symptoms has slightly worsened after they had used the pharmacogenetic report to guide treatment.

Discussion: There is emerging evidence that preemptive genetic testing for numerous gene & psychiatric-drug pairs has reached levels for clinical utility which includes validation of analytical and clinical validity. Genetic testing has become readily available but however clinicians and patients are poorly prepared to this new emerging field and proper education is of utmost importance. This presentation will review the level of evidence for 'actionable' gene-drug pairs in psychiatry in addition to present novel genomic findings and reports from our ongoing genetic testing experiences.

S223. COMBINED TREATMENT WITH A SELECTIVE PDE10A INHIBITOR TAK-063 AND ANTIPSYCHOTICS AT SUBEFFECTIVE DOSES PRODUCES POTENT ANTIPSYCHOTIC-LIKE EFFECTS WITHOUT EXACERBATING SIDE EFFECTS PROFILE IN RODENTS

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Background: Activation of indirect pathway medium spiny neurons (MSNs) via promotion of cAMP production is the principal mechanism of action (MOA) of current antipsychotics with dopamine D2 receptor antagonism. Phosphodiesterase 10A (PDE10A) inhibitors activate both direct and indirect pathway MSNs by increasing both cAMP and cGMP levels by inhibiting their degradation, which might be expected to promote activation of intracellular signaling similar to that of D2 antagonists in the indirect pathway MSNs. Thus, the activation of the indirect MSN pathway through the distinct MOA of these compounds raises the possibility of augmented pharmacologic effects with combined treatment.

In this study, we compared gene-regulation patterns in the indirect pathway MSNs induced by the PDE10A inhibitors T-773 and T-609, and the D2 antagonist haloperidol, using a cell-type-specific comprehensive gene expression analysis in Drd2-bacTRAP (translating ribosome affinity purification) mice. The pharmacologic effects of combined treatment with another PDE10A inhibitor, TAK-063, and clinically used antipsychotics, haloperidol (HAL) and olanzapine (OLA), were evaluated in multiple rodent models.

Methods: Male ICR mice, Drd2-bacTRAP mice, and Sprague-Dawley rats were used. The indirect pathway MSN-specific gene expression changes by T-773, T-609, and HAL were investigated using RNA sequencing of striatal samples of Drd2-bacTRAP mice. The activation of MSNs in rats was evaluated by measuring glutamate receptor subunit 1 phosphorylation (pGluR1) levels. An in vitro electrophysiological study on the corticostrial pathway in rats was conducted in a slice preparation. The activation of each MSN pathway was assessed by inducing genes as pathway-specific markers: enkephalin for the indirect pathway and substance P for the direct pathway. Suppression of MK-801- or methamphetamine (METH)-induced hyperactivity was assessed by measuring locomotor activity for 2 hours after administration of these stimulants to rats. Improvement of prepulse inhibition (PPI) was investigated in a MK-801-induced PPI deficit mouse model.

Results: Translational profiling in Drd2-bacTRAP mice treated with the PDE10A selective inhibitors, T-773 and T-609, and with HAL suggested regulatory of a largely overlapping signaling pathway by these compounds in the indirect pathway MSNs: 87% of the genes regulated by HAL were also regulated by both T-773 and T-609. Combined treatment with TAK-063 and either HAL or OLA produced an augmented effect on pGluR1 in the rat striatum. An electrophysiological study in rat brain slices indicated that TAK-063 enhanced synaptic responses to a similar extent in both direct and indirect pathway MSNs. Additional evaluation using MSN pathway-specific markers revealed that coadministration of TAK-063 with HAL or OLA additively activated the indirect pathway, but not the direct pathway. Combined treatment with TAK-063 (0.1 mg/kg p.o.) and either HAL (0.3 mg/kg p.o.) or OLA (3 mg/kg p.o.) at subeffective doses produced augmented effects on