M198. INVESTIGATIONAL Dopamine Antagonists for the Treatment of Schizophrenia

Abstract not included.

M199. Copy Number Variance (CNV) Analysis to Determine Optimal Antipsychotic Dosage in Schizophrenia: A Pilot Study

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Background: The relationship between genetic polymorphisms of antipsychotic drug-metabolizing agents and drug response has been thoroughly investigated and analyzed. However, from a pharmacokinetic standpoint, few studies have explored the relationship between Copy number variants (CNV) and antipsychotic dosage. The aim of the present study is to test the association between antipsychotic dosage and CNV in schizophrenia (SCZ) patients.

Methods: The current dosage of antipsychotic medications was collected from 263 schizophrenia patients. The dosage was standardized using three different methods: chlorpromazine equivalent (CPZeq), defined daily dose (DDD), and percentage of maximum dose (PM %). The patients were then genotyped using the Illumina HumanOmni2.5-8 BeadChip Kit.

Results: The CNV analysis did not show that CNVs are associated with dosage variation for CPZeq, PM %, and DDD.

Discussion: In this pilot sample, we investigated for the first time CNVs and standardized antipsychotic dosage. The relationship between CNV and optimal antipsychotic dosage has far reaching clinical implications. Further analysis is required that utilize large prescription databases to build on the results presented in this pilot study.

M200. Clozapine-Induced Hepatotoxicity: Two Case Reports

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Background: Liver function tests (LFT) abnormalities secondary to antipsychotics (AP) are common, early, and often mild and transient. Up to 60% of patients on clozapine experience an increase in LFT, at medium-range doses (200–400mg), and usually dose-dependent, with spontaneous resolution in half the cases, no dose reduction needed. Fatal outcomes are extremely rare, with an incidence around 0.001%. The hepatotoxic effects of clozapine have received considerable less attention than its cardiometabolic and hematologic counterparts. Consequently, there are few independent guidelines on how to handle such cases. Our objective is to report 2 cases of mild clozapine-induced liver injury and discuss possible protocols of early detection and management.

Methods: We described 2 cases of clozapine-induced hepatotoxicity in patients with schizophrenia.

Results: CASE 1: 33 y/o, male, caucasian, 5y of illness. Had previously used risperidone and paliperidone, and was currently taking olanzapine, without good response. Clozapine 25mg/d was introduced – in addition to olanzapine 15mg/d – with a 25mg increase every 2d. On D12 of clozapine (150mg/day), he reported nausea, diarrhea and dizziness, worsening the next few days, with confusion and choloria. Blood tests detected increases of ALT (242U/L), serum bilirubin (total 1.59mg/dL; direct 1.29g/dL; indirect 0.3mg/dL) and ESR (60mm/1sth). He was admitted and AP were interrupted. After 48h, presented full clinical recovery. Leukocyte blood count and ESR were still high in the first week, but LFT and bilirubins progressively decreased. All exams normalized in 1m. After 2w, olanzapine was reintroduced, with no LFT changes.

CASE 2: 48 y/o, female, caucasian, 15y of illness. Partial response to risperidone and olanzapine. 20d after clozapine was introduced (75mg/d), she reported nausea, vomiting, choloria, abdominal pain and headache. Presented elevated AST (881U/L), ALT (771U/L), CK (732U/L), GGT (141U/L) and ALP (161U/L), decreased Hb (9.6g/dL), mild leukocytosis (10,800/mm3), mild leukocyturia and hematuria, though bilirubin and platelet levels were normal. Clozapine was immediately suspended and olanzapine 10mg/d reintroduced progressively, maintaining partial remission of positive symptoms. Blood counts and LFT were normalized within 1m and no hospitalization was required.

Discussion: Both cases illustrate different presentations of hepatotoxicity by clozapine. Case 1 had no LFT dosage before the introduction and no indicative hepatic risk. With a regular dose evaluation, developed a severe hepatic injury. Case 2 had a history of side effects to previous antipsychotics. She started with normal LFT levels and evolved with mild hepatic injury due to the slow dose increase.

In both cases LFT weren’t requested periodically until clinical symptoms emerged. At this point, it was fundamental to instruct the patient to report any warning clinical signs. A serialized LFT protocol wouldn’t show benefits to prevent hepatotoxicity in the outcome of our cases. However, some authors recommend monitoring them 4–6m after starting AP, specially the first 4–5w, since it could predict a bad outcome of severe hepatitis. Previous studies point ALT>3ULN or ALP>2ULN or any rise of transaminases with CK or bilirubin altered as sensitive markers for liver damage. In such cases, the AP should be suspended.

There is no consistent data regarding the indication of clozapine rechallenge after hepatotoxicity. Yet, the early onset of drug injury (1–6w) and the rapid rise in ALT on rechallenge might be a contraindication of a new try or continuous use of the drug.

Considering guidelines on clozapine induced hepatotoxicity are not clear, we suggest the topic to be revisited and better established.

M201. Moderators of Weight Gain in Randomized Controlled Trials of Schizophrenia – A Meta-Regression Analysis

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Background: Weight gain is an important side effect of antipsychotics. Meta-analyses of randomized controlled trials indicate differences between the multiple antipsychotics in propensity to cause weight gain. However, antipsychotic-associated weight gain, in randomized controlled trials as well as in real life situations, might also depend on population characteristics and treatment-related factors.

As a preparatory work for a systematic review and network-meta-analysis on metabolic side effects of antipsychotics (presented in another poster at this conference), we conducted a meta-regression analysis of potential moderators of weight gain.

Methods: We selected acute phase short-term, acute phase long-term as well as relapse prevention studies (all found by systematic reviews conducted by...
our group in the past) from our database of randomized controlled trials of antipsychotics in schizophrenia. We conducted

i) meta-regression-analyses based on pairwise meta-analysis of the mean difference (MD) in change in weight (kg) between patients exposed to antipsychotics and placebo, and

ii) meta-regression-analyses based on single-arm meta-analysis of the change in weight (kg).

We examined the moderators baseline weight, study duration, percentage women, and publication year. We conducted the analyses for all drugs pooled, placebo and per individual drug. For presentation of the results we focus on the drugs aripiprazole, haloperidol, quetiapine, olanzapine, and risperidone, because these are popular drugs in clinical practice, they differ in their receptor-binding profiles and multiple studies are available for these drugs. We conducted the analysis in R using the commands metacont, metagen and metareg from the package meta.

**Results:** The dataset comprises 603 randomized controlled trials with 141 584 patients that examined 40 different antipsychotics. Trial duration varied between 3 and 156 weeks (median 8 weeks). 168 studies with 49 670 patients reported on change in body weight. We found no effect of baseline weight on antipsychotic-associated weight gain, however on placebo, lower baseline weight was associated with more weight loss. Moreover, on antipsychotics, higher percentage of women was associated with less weight gain, and, on placebo, higher percentage of women was associated with more weight loss. Longer study duration was not associated with increased weight gain. On placebo, longer studies were associated with more weight loss. There was no effect of publication year.

**Discussion:** Surprisingly, we found no moderating effect of baseline weight and study duration on weight gain. However, our data suggests that men and women could have different risk of weight gain. Moreover, weight loss after switching to placebo might be higher in women and patients with less baseline weight. For interpretation, it must be noted that meta-regressions are observational evidence and thus prone to confounding. In addition, the scatter plots, presented on the poster, need to be considered to judge the robustness and magnitude of the moderated effects. Additional meta-regressions (planned to present on the poster) should address further potential moderators, such as antipsychotic dose, ethnicity, previous antipsychotic exposure and dropout rates.

**Poster Session II**

**S213**

**M202. SEX-RELATED DIFFERENCES IN CLOZAPINE SIDE EFFECTS IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA**

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**Background:** Treatment resistant schizophrenia (TRS) affects up to 30% of patients with psychosis and is a major cause of disability. Although clozapine is the only indicated drug for TRS, it is largely underused, partially due to its life-threatening adverse effects (AEs) as agranulocytosis and myocarditis. However, clozapine treatment is also burdened by other AEs as constipation, hypersalivation, postural hypotension, tachycardia, metabolic abnormalities and weight gain. In recent years many efforts have been made to outline clinical and neurobiological characteristics of TRS. Although sex is one of the most relevant factors accountable for the clinical variability of schizophrenia, literature on sex differences in clozapine’s tolerability is still limited. Studies showed that women experience more often than men weight gain, hyperglycemia and constipation. Conversely, hypertension and dyslipidemia seem more frequent in men. Based on these premises, our study aimed to investigate sex differences in prevalence of clozapine’s chronic AEs in TRS patients.

**Methods:** We performed an observational cross-sectional study with TRS on 147 patients, 93 males and 54 females with at least two-year clozapine treatment. We assessed metabolic status and AEs by interviews, collection of clinical data (BMI, waist circumference, blood pressure and heart rate) and blood tests including lipid profile, fasting glucose and HbA1c. Chi-square analysis was used to investigate the association between sex and clozapine AEs (tachycardia, postural hypotension, constipation, hypersalivation and metabolic syndrome). Multiple logistic regression analyses were performed to further analyze the relationship between sex and AEs considering the role of possible confounding factors as plasmatic concentration, oral dosage, number of daily administration, age and duration of therapy.

**Results:** We found a higher prevalence of tachycardia in males (p=0.034, χ²=4.49) and of orthostatic hypotension (p=0.01, χ²=6.70) and constipation (p=0.01, χ²=6.45) in females. Logistic regressions showed that male sex was the only significant predictor of tachycardia (p=0.01), while female sex predicted hypotension (p=0.04) and constipation (p=0.03). Although no differences emerged for hypersalivation and metabolic syndrome (MetS), Chi-square showed significant differences in prevalence for two MetS criteria: hypertriglyceridemia (56.94% in men, 29.79% in women, p=0.003, χ²=8.43) and central obesity (83.33% in men, 97.44% in women, p=0.03, χ²=4.69).

**Discussion:** Consistent with previous literature, our study showed sex differences in prevalence of chronic clozapine’s AEs. Although perceived as minor AEs, hypotension, constipation and tachycardia could affect patient’s quality of life, cause treatment discontinuation or increase mortality. In particular, postural hypotension and tachycardia have been associated with an increased risk of all-cause death and cardiovascular events in the general population. Clozapine-related constipation can develop into full-blown ileus in up to 2.1% of cases, a higher, more durable and more dangerous risk than agranulocytosis. Finally, hypertriglyceridemia and central obesity are well known cardiovascular risk factors. Our study suggests clinicians should carefully monitor for clozapine’s AEs also considering sex, in order to early detect them, promptly treat them and prevent severe complications. Literature suggest some of the sex differences reported in schizophrenia may be due to the protective role of estrogens. Further studies, with a particular attention to hormonal status, could contribute to better understand the pathophysiology of sex differences in TRS and define a personalized therapeutic approach.

**M203. ANTIPSYCHOTIC-LIKE EFFECT OF DOXYCYCLINE IN PSYCHOTOMIMETICS SYMPTOMS INDUCED BY AMPHETAMINE**

Abstract not included.

**M204. ULTRA-RESISTANT SCHIZOPHRENIA IS ASSOCIATED WITH A DELAY TO INITIATE CLOZAPINE AND WITH LESS ABDOMINAL OBESITY. SEX DIFFERENCES IN INSULINEMIA AND LEPTIN LEVELS ARE OBSERVED BETWEEN RESPONDERS AND NOT RESPONDERS**

Guillermo Höning, Demián Rodante, Federico Daray, Mercedes Izaguirre, Mariela Lenze, Joaquín Valentini, Facundo García Bournissen, María Laura Gutiérrez, Silvia Wikinski