a challenge for their treating physicians and although many augmentation strategies have been tried, including other agents with antipsychotic properties, mood-stabilizers, antidepressants, glutamatergic agents and neuromodulation techniques. 

Methods: A literature review was conducted in the main electronic databases (PubMed, Cochrane, EMBASE, CINAHL), and papers published between January 2000 and August 2019 were included. The search paradigm was “ultra-resistant schizophrenia” or “clozapine-resistant schizophrenia” or “add-on to schizophrenia” and non-proprietary names of currently marketed antipsychotics, mood stabilizers, antidepressants, nootropics, “neuromodulation techniques” and “psychotherapy”.

Results: A number of 197 papers resulted from the primary search, and 45 papers remained after de-duplication and application of inclusion and exclusion criteria. Electroconvulsive therapy seems to be efficient and the response rate ranges from 37.5 to 100% in cases of ultra-resistant schizophrenia [1]. Transcranial direct-current stimulation (tDCS) lead to meaningful improvement in positive symptoms and overall symptomatology when compared to no standard treatment of the control group, in a 4 weeks trial [2]. A 21-week pragmatic trial did not find any significant lasting effect of the cognitive-behavioral therapy (CBT) on total symptoms of schizophrenia compared to treatment as usual, although improvements were detected [3]. Pharmacological augmentation of clozapine included amisulpride (results were not significant), memantine (positive effects, but the trial included a small number of patients), reboxetine (uncertain efficacy), ziprasidone (possible effective on negative and cognitive symptoms), aripiprazole (uncertain effect based on multiple trials), lamotrigine (not efficient), pimozide (not efficient), sertindole (no benefits detected, possible worsen psychosis in several cases), tetrabenazine (not effective), duloxetine (possible efficacy on negative and general psychopathology, but not on the executive cognitive functions), topiramate (no efficacy), valproic acid (possible efficacy, larger trials needed), risperidone (not efficient), donepezil (not efficient), mirtazapine (possible efficacy), sulpiride (possible efficacy in a subgroup of schizophrenia patients).

Discussion: Until now no single pharmacological augmentation strategy to clozapine has been proven superior to other in double-blind randomized, large-scale placebo-controlled data. Electroconvulsive therapy seems to be the only non-pharmacological technique with enough data to support its efficacy in ultra-resistant cases of schizophrenia. Other neuromodulatory techniques, like tDCS, are still in early phase of investigation, and psychotherapy does not have enough evidence to support its efficacy.

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T198. CAN AUGMENTED SUBLINGUAL OXYTOCIN DECREASE NEGATIVE SYMPTOMS WITHIN TREATMENT RESISTANT SCHIZOPHRENIC POPULATIONS: A PILOT STUDY

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Background: The prevalence of schizophrenia in the United States ranges between 0.5% and 1%. This difficult-to-treat disorder is marked by the presentation of symptoms that are both positive (i.e. hallucinations) and negative (i.e. blunted affect), as well as disturbances in cognition and affect. Several second-generation antipsychotics (i.e. olanzapine, risperidone) have been utilized for their varying effects on the symptoms of schizophrenia, yet 20% to 60% of patients with schizophrenia are considered treatment-resistant. While clozapine is shown to be the most effective antipsychotic, negative symptoms commonly persist in clozapine-treated patients. Research shows that oxytocin has neuromodulatory effects on social perception and enhances empathy and attentional engagement in individuals with schizophrenia, suggesting it may have therapeutic effects on negative symptoms. The present study presents a pilot prospective research study evaluating the efficacy of combining clozapine and sublingual oxytocin for the reduction of positive and negative symptoms.

Methods: Prospective research study evaluated 25 treatment resistant schizophrenic patients who were admitted to the persistent psychotic disorder unit at a private hospital, with an average treatment duration of 2.9 months with a range between 1 and 9 months. All have been followed as outpatient for up to 30 months after discharge. All patients were 18 years or older and met the DSM-5 criteria for schizophrenia. The Positive and Negative Syndrome Scale (PANSS) was used to assess the efficacy of the combination treatment. Clozapine was prescribed to all 25 patients after they had failed to improve in three different trials of other antipsychotic medications. Sublingual oxytocin (10 IU 2x per day; 20 IU 3x per day) was prescribed to 25 of the patients only after the improvement in positive symptoms on the PANSS with clozapine had plateaued. Due to a history of intranasal substance use in all the patients, oxytocin was administered sublingual to ensure adequate and less variable absorption of the neuropeptide.

Results: A time-series analysis demonstrated a significant decrease in PANSS scores across admission, stabilization of clozapine and stabilization of oxytocin (p <.02) with the overall average PANSS score on admission was 102; after stabilization on clozapine, the average score decreased to 68. After administration oxytocin (8 weeks) the average score decreased further to 47 and improved PANSS score were not related to serum clozapine levels. Clinical and family notes indicated clinically meaningful improvements in affect, eye contact, and ability to socialize. These gains have been sustained over the full range of our observations. Families self-reported an increased ability to participate in social roles and activities.

Discussion: The combined effect extends the current research of augmenting sublingual oxytocin and clozapine for individuals with previously treatment-resistant symptoms. Though each patient benefited from clozapine alone, negative symptoms persisted. Patients, their families, and treatment program staff all observed a significant reduction in the patients’ anxiety and an improvement in the patients’ relatedness. While this case series cannot establish that oxytocin is responsible for the clinical improvements seen here, it does suggest that it may improve negative symptoms and social functioning in patients with treatment-resistant schizophrenia showing incomplete improvement with clozapine alone. The present study suggests the need for future research to explore the possibility that oxytocin can mitigate the negative symptoms of schizophrenia.

T199. 7% WEIGHT CHANGE ASSOCIATED WITH ANTIPSYCHOTICS: A META-ANALYSIS

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Background: In recent years, antipsychotic-induced weight gain (AIWG) has gained more attention in research. Although interventions to prevent weight gain are currently being investigated, AIWG remains a major problem for both patients and clinicians and often results in poor treatment adherence, a decrease in quality of life. Furthermore, schizophrenia is associated with higher mortality rates and a decreased life expectancy. Recently, some new antipsychotic drugs have been introduced that are hypothesized to entail no or low incidences of clinically relevant weight gain (CRWG), and high incidences of clinically relevant weight loss (CRWL). Here ‘clinically relevant’ is defined as >7% weight change. In this meta-analysis, we
aim to give a complete overview of both CRWG and CRWL, including these newer antipsychotics.

**Methods:** We searched Pubmed, Embase and Psychinfo for randomized clinical trials of antipsychotics that reported 7% weight change in study populations aged 18 years or older. We performed meta-analyses stratified by study duration (≤6 weeks, 6–16 weeks, 16–38 weeks and >38 weeks) with a random effects model.

**Results:** The search yielded in total 941 articles. Ninety-two articles could be included in the meta-analysis, resulting in 341 records in the data set. All data were related to AP switch patients, no data on AP-naïve patients were found. Preliminary results showed that haloperidol, paliperidone and quetiapine had relatively low CRWG (16.6%, 18.7% and 18.4%, respectively), aripiprazole and risperidone had relatively high percentages of CRWG (25.4% and 24.0%, respectively). Olanzapine (29.5%) and lurasidone (7.4%) resulted in respectively the highest and lowest CRWG at >38 weeks of treatment. In the placebo group, CRWG was 3.8%. Incidences of CRWG continued to rise even after 38 weeks of treatment in most treatment groups.

CRWL occurred with all antipsychotic drugs; at 6–16 weeks aripiprazole (7.9%) and ziprasidone (7.1%) had CRWL similar to placebo (8.7%). We found insufficient data on CRWL in the long term (>38 weeks) to draw any conclusions.

**Discussion:** All antipsychotics can result in both weight gain and weight loss. Previous research showed that patients more often gain weight than lose weight (Bak, 2014) and this is replicated in the present meta-analysis. Proportions CRWG and CRWL seem different between the antipsychotics. Future network meta-analysis are needed to test statistical significance of those differences. It appears, however, that CRWG is higher in patients receiving antipsychotics drugs compared to placebo. No conclusions can be drawn on CRWL due to insufficient data. It is clear that after >38 weeks of treatment, no ‘plateau’ phase is reached as CRWG continued to increase. More future research is needed on long-term weight effects on both CRWG and CRWL to give a clear overview on the ‘real’ effects on weight, as the majority of studies had a duration of less than 26 weeks. Furthermore, more research is needed on the long-term dose-response relationship in CRWG, as this could prove to be a method for managing weight in some patients.

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**T200. METABOLIC SIDE EFFECTS OF ANTIPSYCHOTIC DRUGS – PROTOCOL OF A SYSTEMATIC REVIEW AND NETWORK-METAANALYSIS**

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**Background:** Antipsychotic drugs are the mainstay of the pharmacological treatment of schizophrenia, used in the acute episode of the disorder and for prevention of relapses. Unfortunately, antipsychotics cause side effects. Weight gain is one of the most prominent side effects. In line with weight gain, also alterations of lipid- and glucose homeostasis can occur and increase the risk for cardiovascular disorders. So far, the differences between the multiple antipsychotics in propensity to cause these alterations have not been examined based on data from randomized controlled trial. Therefore, we are conducting a systematic review and network-metanalysis on metabolic side effects of antipsychotic drugs.

**Methods:** Systematic review and network-metanalysis.

**Population:** Patients with schizophrenia.

**Interventions:** Antipsychotic drugs and placebo.

**Comparator:** In network-metanalysis all interventions are compared with each other. For presentation of Results., placebo will be used as reference.

**Outcomes:** The primary outcomes will be continuous change of body weight. Additional outcomes will be continuous change of blood glucose, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol as well as dichotomous values of these outcomes (i.e. number of patients with a clinically relevant increase over pathological thresholds).

**Statistical analysis:** Network-metanalysis.

**Study design:** Randomized controlled trials.

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**T201. EFFECTS OF PALIPERIDONE PALMITATE ON HEALTHCARE UTILIZATION AND COSTS FOR PATIENTS WITH SCHIZOPHRENIA: A CLAIM-BASED MIRROR-IMAGE STUDY IN SOUTH KOREA**

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**Background:** Long-acting injectable (LAI) antipsychotics, such as paliperidone palmitate (PP), are known to improve treatment adherence in patients with schizophrenia, which can lead to reductions in relapse and hospitalization rates. However, relatively few studies have demonstrated the economic impact of LAIs, especially in Asian populations.

**Methods:** We conducted a claim-based mirror-image study to explore changes in healthcare utilization and associated costs, among 1,272 South Korean patients with schizophrenia (ICD-10-CM code F20), between the 1-year periods before and after the initiation of PP treatment.

**Results:** The results showed that patients accessed outpatient services more frequently after versus before starting PP treatment, with the number of prescription days increasing by 133.45 (p < .0001) and the associated costs increasing by USD 1,497.15 (p < .0001). In contrast, the number of admission days was reduced by 11.33 after starting PP treatment (p < .0001) and the associated costs were reduced by USD 1,220.75 (p < .0001).

**Discussion:** Although the high acquisition cost of PP has been regarded as an obstacle to its clinical use, our results imply that the high prescription costs for PP may be counterbalanced by the reduced admission costs associated with its use. Economic outcomes for patients treated with LAIs should be investigated further to help healthcare decision-makers and providers to determine the value of LAIs relative to other treatment medications.

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**T202. THE EFFECT OF ANTIPSYCHOTIC DRUGS ON MEMBRANE FUSION: AN IN VITRO STUDY**

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