Well-being and co-morbidity in recent onset schizophrenia  
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Summary
This thesis consists of three parts concerning (co-morbidity in) recent onset schizophrenia; the studies were executed in adolescents and young adults with recent onset psychosis, during the use of antipsychotic medication as well as in neuroleptic naïve patients.

Subjective well-being, craving for and use of cannabis during treatment with antipsychotic medication, as well as the effects on continuation of this treatment, are described in Part I.

The emergence and severity of obsessive-compulsive symptoms in olanzapine and risperidone, as well as the relationship between catechol-o-methyltransferase gene and obsessive-compulsive symptoms were studied in patients with recent onset psychosis (Part II).

Hepatic and peripheral insulin resistance were studied in neuroleptic naïve patients and healthy controls by a detailed study of glucose metabolism with stable isotopes (Part III).

The following pages give a summary of the findings and limitations of the research described in this thesis.

Part I. Antipsychotic medication, subjective well-being, craving for and use of cannabis and continuation of treatment with antipsychotic medication

Chapter 1.1 Adolescence, schizophrenia and drug abuse: a window of vulnerability

A literature overview of the relationship between adolescence, schizophrenia and drug abuse is presented in Chapter 1.1. This overview shows that dysphoria and anhedonia in adolescent patients with schizophrenia are important factors in treatment with antipsychotic medication, both in terms of patient’s satisfaction and in the prevention of substance abuse.
Chapter 1.2 Effect of olanzapine and risperidone on subjective well-being and craving for cannabis in patients with schizophrenia or related disorders: a double blind randomized trial

Findings

One hundred twenty eight patients of the 201 eligible patients received at least 1 dose olanzapine (n= 63) or risperidone (n=65), of whom 41 (32%) were using cannabis at baseline. There was no significant difference in estimated D₂ receptor occupancy between the groups. The largest increase in subjective well-being took place in the first week of the trial. None of the main effects (subjective well-being, use or craving for cannabis) differed statistically significant between groups using olanzapine or risperidone.

Limitations

- Only 41 of the 128 patients were using cannabis at baseline, resulting in limited statistical power for the detection of differences in changes in craving and cannabis use.
- The cannabis using olanzapine group had a significantly lower score on an instrument to measure craving than the cannabis using risperidone group (despite randomization).
- Only 64% of the eligible patients were willing to participate in the study, possibly limiting the external validity of the study.

Chapter 1.3 Early withdrawal in a double-blind randomized clinical trial with olanzapine and risperidone performed in adolescents with first psychosis

Findings

24% of the included patients, halfway the trial, terminated the double blind phase before the end of the determined 6 weeks. Reasons for drop out suggested that the double blind aspect of the trial led to higher drop out rates, especially for patients with paranoid delusions.
Chapter 1.4 Effect of early dysphoric response and cannabis use on discontinuation of olanzapine and risperidone in young adults with recent onset schizophrenia and related disorders

Findings
After one year follow up, 75 of 113 patients (66%) had discontinued the treatment. Mean time to discontinuation was 5.8 (SD 4.9) months, with no significant difference between olanzapine (5.6 months, SD 4.9) and risperidone (5.9 months, SD 4.9). However, patients with an early (relatively) dysphoric response discontinued medication (mean 4.1 months, SD 4.4) significantly earlier than those with no early (relatively) dysphoric response (mean 7.3 months, SD 4.8; log-rank chi squared= 13.3, d.f. =1, P =0.0003). In addition, patients using cannabis discontinued medication significantly earlier (mean 4.3 months, SD 4.2) compared to the non-users (mean 6.4 months, SD 5.0; log-rank chi squared= 4.98, d.f. =1, P =0.03). No significant interaction effects for early dysphoric response or cannabis use and medication were observed.

Chapter 1.5 Improvement of subjective well-being and enduring symptomatic remission, a 5 year follow up of first episode schizophrenia

Findings
Patients with Enduring Symptomatic Remission (ESR) (n=30) had a higher mean improvement of subjective well-being during early treatment as assessed with the Subjective Well-being under Neuroleptics (SWN) than those without ESR (n=74) (p=0.004). Early symptomatic improvement as assessed with the PANSS was not related to ESR (p=0.95).

Limitations
It is unknown whether improving early subjective well-being is related to ESR.
Summary

Part II. Obsessive-compulsive symptoms in recent onset schizophrenia

Chapter 2.1 Obsessive-compulsive symptoms in a randomized double blind study with olanzapine or risperidone in young patients with early psychosis

Findings

122 patients were included in the analysis. At baseline, 74 patients had no obsessive-compulsive symptoms, in 10 of them OCS emerged after 6 weeks, with no differences between olanzapine and risperidone. In the total group (n=122) and in the group with Y-BOCS scores >0 (n=58), decreases in Y-BOCS scores during treatment were significantly larger in the olanzapine group than in the risperidone group. Also in patients with clinically significant co morbid OCD at (Y-BOCS score >10); n=29), mean reductions in Y-BOCS scores were significantly larger in the olanzapine group than in the risperidone group.

Limitations

- Treatment lasted only for 6 weeks, therefore eventual effects of super sensitivity of the 5 HT2a receptor could not be observed.
- The small sample sizes of some of the subgroups

Chapter 2.2 The catechol-o-methyltransferase gene and obsessive-compulsive symptoms in patients with recent onset schizophrenia

Findings

Severity of obsessive-compulsive symptoms in 77 male patients with recent-onset schizophrenia was assessed using the Y-BOCS and the COMT Val158Met polymorphism was genotyped for these patients. We found a significant effect of COMT genotype on Y-BOCS scores: the Val/Val genotype was associated with highest Y-BOCS scores, whereas patients with Met/Met genotype had lowest Y-BOCS scores. Our data suggest that the COMT high-activity Val allele is associated with more obsessive-compulsive symptoms in young patients with schizophrenia. These results support the hypothesis that the COMT Val158Met polymorphism may be a modifier gene for the symptomatology of schizophrenia.
Limitations

- Sample size is relatively small.
- Genetic heterogeneity of the sample.
- OCS could have been induced by antipsychotic medication, however in this study no difference in the use of olanzapine and clozapine between genotype groups was observed, therefore we do not think this to be a confounding factor.
- Our analyses included only male patients with schizophrenia; future studies should investigate whether COMT genotype has similar effects on OCS in female patients with schizophrenia.

Part III. Insulin resistance in neuroleptic naive patients with recent onset schizophrenia

Chapter 3.1 Hepatic insulin resistance in untreated first episode schizophrenic, schizo-affective patients, a detailed study of glucose metabolism with stable isotopes

Findings

Antipsychotic-naive, first-episode psychotic patients displayed significant hepatic insulin resistance. Peripheral insulin sensitivity did not differ from matched controls. This finding could not be explained by differences in intra-abdominal fat, plasma FFA, glucoregulatory hormones, plasma adiponectin, or plasma RBP4 concentrations.

Limitations

Patients and controls in our study were not matched for dietary intake, or for smoking or exercise patterns. This may be a confounding variable because smoking may affect insulin sensitivity.