Well-being and co-morbidity in recent onset schizophrenia
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General discussion, conclusions and implications
In this thesis a series of studies is presented covering different aspects related to pharmacological treatment of - and co-morbidity in patients with recent onset psychosis: 1. effect of antipsychotic medication on subjective well-being and its consequences, 2. effect of antipsychotic treatment on obsessive–compulsive symptoms, and 3. insulin resistance in antipsychotic naïve patients. The studies were carried out in patients in the Adolescent Clinic of AMC/de Meren (Amsterdam), the Erasmus Medical Center (Rotterdam), Parnassia Psycho Medical Centre (The Hague), Mediant Medical Centre (Enschede), and the department of Endocrinology in the AMC (Amsterdam). The subjective experience, use of and craving for cannabis and discontinuation of olanzapine and risperidone are described in Part I. Genetic factors associated with obsessive-compulsive symptoms (OCS) and the influence of olanzapine and risperidone on OCS were studied in Part II. Hepatic and peripheral insulin resistance in antipsychotic naive patients with recent onset psychosis was described in Part III. This chapter starts with a brief summary of the findings, the methodological strengths and limitations of the studies and interpretation of findings. It concludes with clinical and research implications and some general concluding remarks.

**Brief summary of findings, limitations and interpretation**

**Part I. Subjective well-being, cannabis and continuation of treatment**

Subjective experience is associated with $D_2$ receptor occupancy (de Haan et al 2000, 2003). Atypical antipsychotic drugs with faster dissociation from the dopamine $D_2$ receptor are assumed to induce less negative symptoms and fewer motor side effects (Kapur et al 2001). In addition, they are hypothesized to result in better subjective experiences. Because olanzapine dissociates faster from the dopamine $D_2$ receptor than risperidone, it was hypothesized that olanzapine would be associated with better subjective well-being and less craving for cannabis than risperidone when tested on doses that lead to comparable $D_2$ receptor occupancy in both treatment groups.

In our study on subjective well-being (chapter 1.2), comparing olanzapine and risperidone we used the short version of the Subjective Well-being under Neuroleptics scale (SWN/sv). In the past, the psychometric qualities of the SWN/sv in patients with recent onset schizophrenia during treatment with olanzapine and risperidone were confirmed by our group (de Haan et al 2002). An advantage of
this instrument is its feasibility: not time consuming and no training required. All patients also filled out the Cannabis Use Self Report (CUSR) and Drug Use Self Report (DUSR). These self-rating scales measure cannabis and other drug use in the past month. The validity of self reported drug use data were confirmed by Recent Drug Use Urine analysis (chapter 1.2). All patients with self reported cannabis use at baseline had to fill out two different craving questionnaires; the Obsessive Compulsive Drug Use Scale (OCDUS), a self rating scale consisting of 11 items with a five point Likert type rating measuring drug craving in the past seven days (Franken et al 2002), and the Drug Desire Questionnaire (DDQ), a self rating scale measuring instantaneous craving (Franken et al 2002), both with good reliability and concurrent validity.

In the RCT the hypothesis that olanzapine would be associated with better subjective well-being and less craving for cannabis than risperidone was rejected: there were no significant differences between the treatment conditions in outcome with respect to changes in subjective well-being or in the reduction of craving for cannabis or in use of cannabis. These findings corroborate the conclusions of a previous cross sectional study showing high levels of subjective tolerability for both olanzapine and risperidone, and few differences between the two medications (McGrath et al 2005). These findings underscore the importance of including an adequate control condition in studies comparing different antipsychotic medications. For example, some recent placebo controlled studies examining the craving for substances, showed reductions in craving for cocaine under risperidone (de la Garza et al 2005, Smelson et al 2002, 2004), whereas olanzapine was associated with both reductions in craving (Hutchison et al 2001, 2004, Smelson et al 2006) and an increase in craving (Kampman et al 2003). However, in a 14-week double blind study comparing the efficacy of olanzapine to risperidone in reducing substance craving in individuals with schizophrenia (Akerele et al 2007), craving for cannabis was more likely in the risperidone group than in the olanzapine group.

Strengths of our study comparing olanzapine and risperidone are the randomized double blind design and the relatively high number of patients with recent onset psychosis that were included. Therefore the methodological quality and power to find differences between olanzapine and risperidone was adequate.

A limitation of this study is that only 64% of the eligible patients were willing to participate in the study, possibly limiting the external validity of the study. However, we did not find significant differences in patients that refused participation compared to those who were randomized. Still, we have no measurements of subjective well-being in the group that refused participation and therefore we cannot exclude selection bias. Another limitation is that only 70% of the participating patients completed the 6-week treatment. However, high discontinuation rates in studies
with antipsychotics are common, especially in adolescents and young adults with recent onset schizophrenia. Another limitation of the study is that only 41 of the 128 patients in the study were using cannabis at baseline, resulting in limited statistical power for the detection of differences in changes in craving and cannabis use. One could also argue that if the randomized part of the trial had been extended beyond 6 weeks, differences in primary outcomes would have been found. However, the fact that most of the changes in SWN and OCDUS scores took place within the first week of the trial renders this explanation for the lack of differences in primary outcome variables unlikely.

The most likely conclusion of chapter 1.2 is that our hypotheses were not correct. Probably, the difference in dopamine dissociation between olanzapine and risperidone is too small to generate differences, or differences in dopamine dissociation are not related to differences in subjective experience or craving for cannabis at least at when both olanzapine and risperidone are given in doses that lead to comparable dopamine D₂ receptor occupancy levels.

Halfway the first phase of the study we found that many patients (24%) discontinued the study medication in the first 6 weeks (chapter 1.3). This is in line with the literature showing high dropout rates in double blind studies among adolescents with a first psychosis frequently in combination with substance abuse and paranoia (Kranzler et al 1996, Margittai et al 1986). However, early dropout may also be associated with an early dysphoric response to antipsychotic medication may be important in discontinuation of treatment. This was described in chapter 1.4.

In chapter 1.4 is described that early dysphoric response and baseline cannabis use were associated with early discontinuation of antipsychotic medication in the one-year follow-up period. No significant differences in discontinuation rates or time to discontinuation were found between olanzapine and risperidone, and both groups reported a similar increase in subjective well-being in the first phase. Discontinuation rates in our study were comparable with those in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (Lieberman et al 2005), but higher than in the recent Schizophrenia Outpatient Health Outcomes (SOHO) study (Haro et al 2007). We could not confirm the finding in the CATIE study that time to discontinuation of treatment for any cause was longer in olanzapine than in the risperidone group. Differences in population may account for these differences in findings, since the CATIE study was performed in patients with chronic schizophrenia and doses of medication were higher than in our study. In a comparison study of atypical antipsychotics in the treatment of first-episode psychosis, risperidone (mean dose 2.4 mg/day) and olanzapine (mean dose 11.7 mg/day) had equivalent rates of discontinuation during one year, about 70%, comparable to our results (Marx, 2005). The current study does confirm previous studies reporting a
negative relationship between early dysphoric response and treatment continuation (De Millas et al 2006, Garavan et al 1998, Karow et al 2007, Naber et al 2001). It should also be mentioned that subjective well-being is not the only predictor of medication continuation or adherence. Other studies report an association between negative attitudes towards medication and poor cognitive performance, particularly of working memory (Goodman et al 2005) and that relationships with clinicians appeared to be an important determinant of patients’ attitudes toward treatment and adherence to medication (Day et al 2005).

The finding that baseline cannabis use predicted earlier discontinuation of antipsychotic medication, confirms previous findings (Coldham et al 2002, Kamali et al 2006, Lambert et al 2005, Owen et al 1996). Only one study, in which no doses of atypicals were reported, found that substance misuse showed no significant association with adherence (Mutsatsa et al 2003).

Whether early improvement of subjective well-being is also related to the long term course of schizophrenia, is described in chapter 1.5. The aim of the prospective study in chapter 1.5 was to compare the predictive validity of early improvement in subjective experience and early improvement of rater based symptoms on enduring symptomatic remission (ESR) status. In a previous study it was shown that improvement in early functional, symptomatic and subjective well-being predicts remission during two-year follow up (Lambert et al 2006). This chapter describes how 110 consecutively admitted patients suffering from a first episode of schizophrenia or related disorder were monitored during a 5-year follow-up. It was found that early improvement of subjective well-being was related to ESR in first episode schizophrenia or related disorders.

The conclusion of part I is that improvement of subjective well-being is not only important for (relatively) long-term effects on discontinuation, but also on (relatively) long-term effects on remission of symptoms. There were no significant differences between olanzapine and risperidone when given in doses that lead to comparable dopamine D2 occupancy in outcome with respect to changes in subjective well-being or in the reduction of craving for cannabis or in use of cannabis.

Part II. Obsessive-compulsive symptoms in recent onset schizophrenia

The central question in chapter 2.1 was to determine in young patients with recent onset schizophrenia whether the emergence or exacerbation of obsessive-compulsive symptoms (OCS) differed during treatment with olanzapine or risperidone. Previous reports suggest that both olanzapine and risperidone may either induce or reduce OCS (Alevizos et al 2002, al-Mulhim et al 1998, Alzaid et al 1997, Andrade

In this chapter, obsessive-compulsive symptoms were assessed with an instrument developed for non-psychotic patients. It is sometimes difficult to distinguish between psychotic and obsessive symptoms. We used the following criteria: content of the OCS should not be related to the content of psychosis; patients should be aware that the obsessive thoughts, impulses or ideas were exaggerated and unwarranted. Assuring is that the Y-BOCS has shown good internal consistence and good inter-rater reliability in patients with recent onset schizophrenia (de Haan et al 2006).

Patients with recent onset psychosis showed a significant difference in decrease in Y-BOCS scores with olanzapine leading to larger reductions in OCS than risperidone using low doses (mean 10 mg olanzapine and 2.75 mg risperidone) with similar estimated dopamine D$_2$ receptor occupancy. Conflicting results in previous studies and case reports, regarding the effects of treatment with olanzapine or risperidone on OCS severity might be related to differences in the dosage of medications given. A possible explanation could be that at low doses olanzapine blocks 5HT$_{2a}$ with a lower affinity than risperidone (Marek et al 2003). Differences in neurobiology of primary OCD and co-morbid OCS in schizophrenia could explain the different reactions to antipsychotics (Gao et al 2006), as well as genetic variations. For the frequency of observed OCS the duration of the trial could have made a difference; since eventual effects of supersensitivity of the 5 HT$_{2a}$ receptor could not be observed. This supersensitivity is a factor that might be (partially) responsible for different results after short and longer treatments. Another methodological limitation in our study is that some of the subgroups had small sample sizes; e.g. only 18 patients had moderate OCD.

The study described in chapter 2.2 suggests that high COMT activity is associated with more obsessive-compulsive symptoms in young patients with schizophrenia. We found an association between the high-activity Val allele and more OCS in young males with schizophrenia. Results should be considered preliminary given the relatively small sample size. Another limitation in the sample of the COMT-study is that the analyses included only male patients with schizophrenia, while there are reports of gender specific effects of the COMT genotype (Karayiorgou et al 1999). In this study no differences in the use of olanzapine and clozapine between genotype groups was observed. Therefore we do not think type of medication was a confounding factor in the induction of OCS.
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The overall conclusion of part II is that obsessive-compulsive symptoms in patients with schizophrenia are relatively prevalent, their emergence decreases with the use of olanzapine rather than with risperidone, using low doses. Genetic factors like the COMT genotype play an important role in this co-morbidity of OCS and schizophrenia.

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

The hypothesis of the study in chapter 3.1 was that drug naive first episode patients have pre-existing hepatic and peripheral insulin resistance caused by higher plasma free fatty acid (FFA) (Koutsari et al 2006, Nielsen et al 2004) and altered secretion of adipokines (Cho et al 2006, Combs et al 2001, Fruebis et al 2001, Yamauchi et al 2001). The used method was what is considered to be the gold standard in measuring insulin resistance: the hyperinsulinemic euglycaemic clamp.

Indeed antipsychotic naive patients diagnosed with schizophrenia or schizoaffective disorder showed hepatic insulin resistance more frequently than matched healthy controls. However, this insulin resistance could not be attributed to an increase in visceral fat mass or differences in plasma free fatty acid, adiponectin or RBP4 concentrations.

A limitation in this study was that we did not consider lifestyle factors that might contribute to the development of both schizophrenia and diabetes, such as diet, exercise and smoking (chapter 3.2). Smoking per se may affect insulin sensitivity (Kapoor et al 2005) and could therefore be a confounding variable. However, smoking could be related to an increase in counter-regulatory hormones, but to the best of our knowledge nicotine use has not been associated with selective hepatic insulin resistance. Additionally, a limitation is that it was executed in a small sample. However, the sensitivity and effects size assessed with the executed procedure is high, meaning that even in a small sample differences can be detected.

Instead of changes in counter regulatory hormones, changes in neuronal input to the liver may be responsible for our findings (Demuro et al 2006). Multisynaptic autonomic pathways originating in the brain may be involved in the regulation of hepatic glucose production (Obici et al 2002, Pocai et al 2005) and adipose tissue (Kreier et al 2002). Thus, these findings suggest a direct link between cerebral mechanisms associated with schizophrenia and hepatic insulin resistance.
Summary of clinical and research implications

This thesis showed that early subjective well-being in young patients with recent onset psychosis is an important factor in treatment with antipsychotic medication, both in terms of patient satisfaction and continuation of treatment. Both olanzapine and risperidone were associated with improved subjective well-being, and no evidence was found for a differential effect on subjective experience or on craving for cannabis in doses with to comparable estimated D₂ occupancy. The most likely conclusion is that our hypotheses were not correct. Probably, the difference in dopamine dissociation between olanzapine and risperidone is too small to generate differences, or differences in dopamine dissociation are not related to differences in subjective experience or craving for cannabis. More randomized controlled trials are needed to establish whether different types of antipsychotics really differ in their effect on subjective well-being, craving and drug use behaviour of patients. Another suggestion for further research would be to replicate this trial with low dose first generation antipsychotics such as haloperidol, an effective (and cheaper) D₂ receptor antagonist with potentially equal effects on subjective experience when given in doses which lead to relatively low receptor occupancy.

Early withdrawal in randomized clinical trials is relatively high in a population of patients with first psychosis, and attenuates the generalizability to the target population. Reporting drop-out and reasons for drop out is very important. Time on medication, in the early phase as well as in the one-year follow-up, was shown to be associated with early dysphoric response and baseline cannabis use, but we found no significant differences in treatment duration between olanzapine and risperidone. Improving the subjective response on medication by adjusting dose or type of medication may increase time on medication. We found that subjective experience of improvement during early treatment might identify a group of patients with a better prognosis, since early improvement of subjective well-being was related to enduring symptomatic remission.

In chapter 2.1 we concluded that olanzapine might have advantages over risperidone in the treatment of patients with psychosis and co-morbid obsessive-compulsive symptoms. We speculated that differences in dose of antipsychotics, as well as differences in neurobiology and genetic variation could explain the different reactions to antipsychotics in terms of primary OCD and co-morbid OCD in schizophrenia. With regard to further studies, we recommend that OCS assessments should also be done with a longer duration of study medication and with different doses of antipsychotics. Also, because of these unexplained variations in the effects of treatment with antipsychotics, future pharmacogenetic studies in DRD₂-
DRD$_4$ receptor and 5-HT$_{2A}$ receptor candidate polymorphisms can be recommended as well (Millet et al 2003).

Preliminary data described in chapter 2.2 suggest that the COMT-high activity Val allele is associated with more obsessive-compulsive symptoms in young males with schizophrenia. Future (larger) studies should investigate whether COMT genotype has similar effects on OCS in female patients with schizophrenia.

Finally, chapter 3.2 has shown that antipsychotic-naïve patients with schizophrenia are selectively hepatic insulin resistant. Clinical implication of this finding is that patients should be carefully monitored for glucose changes, especially since treatment with antipsychotics are thought to influence glucose metabolism. Previous studies have demonstrated a crosstalk between the central nervous system on one hand and adipose tissue and liver on the other, coupling central nutrient sensing to peripheral nutrient production (Obici et al 2002). If indeed this crosstalk is disturbed in schizophrenia this may represent a whole new perspective in metabolic research in schizophrenia (Kreier et al 2006). We therefore recommend replication of this study with additional research questions considering lifestyle factors. Lifestyle factors such as diet might contribute to the development of both schizophrenia and diabetes (Peet 1997) and interventions in diet and/or exercise have shown to lead to a significant decrease in the incidence of diabetes over a 6-year period among those with impaired glucose tolerance (Pan et al 1997).

**Concluding remarks**

The studies in this thesis have tried to contribute to the knowledge concerning the well-being of patients with recent onset schizophrenia, in a subjective as well as in a somatic perspective and to find a better insight in factors associated with co-morbidity. The results confirm once again that schizophrenia is a complex and heterogeneous disorder. The problems due to discontinuation of medication due to a dysphoric response, the co-morbidity of substance abuse and obsessive-compulsive symptoms, and the biological predisposition to insulin resistance are only some of the many factors relevant to this group of disorders. Continuing research directed to the many factors involved will hopefully lead to therapeutic opportunities and a higher quality of life in these patients.
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