Well-being and co-morbidity in recent onset schizophrenia
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In the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), schizophrenia is described as “a disturbance that lasts for at least 6 months and includes for at least a month active-phase symptoms (that is, two [or more] of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, negative symptoms).” (Kaplan and Sadock’s, 1998). It is a disorder characterized by three broad types of symptoms, including psychotic symptoms, negative symptoms, and cognitive impairment. Psychotic symptoms involve the loss of contact with reality, including false beliefs (delusions), perceptual experiences not shared by others (hallucinations), or bizarre behaviors. Negative symptoms are deficit states in emotional and behavioral processes. Common negative symptoms include blunted affect (e.g., immobile facial expression, monotonous voice tone), anhedonia (lack of pleasure), avolition or apathy (diminished ability to initiate and follow through on plans), and alogia (reduced quantity or content of speech). Cognitive impairment in schizophrenia exists of decreased attention and concentration, psychomotor speed, learning and memory, and executive functions (e.g., abstract thinking, problem solving) (Mueser and McGurk 2004).

The annual incidence of schizophrenia is 0.2–0.4 per 1000, with a lifetime prevalence of about 1% (Mueser and McGurk 2004).

Schizophrenia usually has a gradual onset between the ages of 16 and 30 years, beginning with the emergence of negative and depressive symptoms, followed by cognitive and social impairment. Several years later follow the emergence of psychotic symptoms and first psychiatric contact. The presence and severity of psychotic symptoms tend to be episodic over time. Negative symptoms and cognitive problems tend to be more stable over time, and contribute significantly to functional impairment. A major goal of treatment is the prevention of relapse of psychotic symptoms, because of their disruptive effects on patients’ lives (Mueser and McGurk 2004).

The aetiology of schizophrenia appears to be consisting from both genetic and environmental factors. Contributing genetic factors appear from evidence that rates of schizophrenia are higher among relatives of patients than in the general population, and the most valid theory until now is that a complex of different genes in interaction with environmental factors underlies the biological susceptibility for the disorder. Among other modifiable biological factors that affect the course of schizophrenia, medication and substance abuse are the most critical. Antipsychotic medications can reduce severity of symptoms and susceptibility to relapses, whereas substance abuse can worsen symptoms and contribute to relapses. Among
psychosocial factors that can influence schizophrenia, stress, coping skills, and social support are most important.

The course of schizophrenia can be understood with the stress-vulnerability model. According to this model, schizophrenia is caused by an underlying psycho-biological vulnerability, determined early in life by genetic and early environmental (e.g. perinatal) effects. This biological vulnerability is hypothesized to consist of structural changes that are likely to result from abnormal early brain development. Schizophrenia is therefore suggested to be a neurodevelopmental disorder.

Once the vulnerability is established, the onset of the illness and its course, including relapses, is determined by the dynamic interplay of biological and psychosocial factors.

In order to influence this course of this deteriorating disorder, major progress in the research into atypical antipsychotic drugs and into psychosocial factors has occurred. Until now, next to psychosocial treatment, antipsychotics have shown to be the mainstay of treatment. Antipsychotics have proven major effects on the reduction of psychotic symptoms and prevention of relapses (Kapur and Seeman 2001) and more modest effects on negative symptoms and cognitive impairment. Before the 1990s, the primary antipsychotics available were the typical or conventional antipsychotics, with the exception of clozapine, an atypical antipsychotic introduced in 1958 but not widely used or available in many places until recently. Since the 1990s, various other atypical antipsychotics have been developed with a different side-effect profile.

One hypothesis about the mechanism of action of atypical antipsychotics, is that fast dissociation from the D₂ receptor modulate the dopamine system in a manner that allows for more appropriate physiological dopaminergic functioning and fewer dysphoric reactions, when used in doses that lead to appropriately high D₂ blockade (Kapur and Seeman 2001).

Dysphoric reaction to antipsychotic medication has received attention recently. Treatment with antipsychotic drugs can have a strong effect on the well-being of patients with schizophrenia and related disorders. In addition, cannabis use, obsessive-compulsive symptoms, and glucose metabolism pathology are important co-morbidity factors that negatively affect the quality of life in these patients, as described in this thesis.

An important characteristic of patients studied in this thesis is the specific life phase; they are adolescents or young adults. Adolescence is the period in human life that is characterized by brain maturation and a transition to independent adult functioning. It is a critical period for the neurodevelopment of brain regions associated with impulsivity, motivation and addiction (Chambers et al 2003), making adolescents and young adults more vulnerable for substance use disorders, but
also for psychotic disorders (Moore et al 2007). Neurocircuitries associated with substance abuse are similar to the ones associated with schizophrenia (Chambers et al 2001), and illicit drugs interact with psychosis by stimulating dopaminergic circuits. Anhedonia (loss of interest in and withdrawal from all regular and pleasurable activities) and dysphoria (an emotional state characterized by anxiety, depression, or unease) are common in adolescents in general (Larson et al 2002). In adolescents with vulnerability for psychosis specifically (Mueser et al 1998), anhedonia and dysphoria are risk factors for substance abuse as well. Also assigning aberrant motivational salience to stimuli plays a role in both psychosis and craving for street drugs (Goldstein et al 2002, Kapur et al 2003). In the following I will briefly review the background of the studies described in this thesis.

Chapter 1.1 of this thesis describes the shared vulnerabilities of adolescents and young adults for the development of schizophrenia and addiction.

As explained before, dysphoria related to the use of antipsychotic medication (neuroleptic dysphoria), is an important factor in the well-being in young patients with schizophrenia. Moreover, initial negative experiences in response to antipsychotic medication probably contribute to the discontinuation of such medications. This is a relevant issue in the treatment of schizophrenia because treatment discontinuation is strongly related to psychotic relapse (Robinson et al 1999). Subjective experiences are correlated with occupancy of dopamine D₂ receptors by the antipsychotic compound (de Haan et al 2000, 2003), and it is suggested that atypical antipsychotic drugs with fast dissociation from the receptor modulate the dopamine system in a manner that allows for more appropriate dopaminergic functioning and fewer negative symptoms and fewer motor side effects (Kapur et al 2001). Olanzapine dissociates faster from the dopamine D₂ receptor than risperidone, and therefore olanzapine is hypothesized to be effective without inducing negative subjective experiences (Kapur et al 2001). However, currently no double blind randomized controlled trials comparing olanzapine and risperidone with subjective experience as the primary outcome-measure are available. Our hypothesis is that treatment with olanzapine in adolescents with first psychosis is associated with a more favourable effect on subjective well-being compared to treatment with risperidone (chapter 1.2).

Neuroleptic dysphoria is hypothesised as a putative mediating factor that contributes to the occurrence of substance abuse co-morbidity in schizophrenia (Baigent et al 1995, Voruganti et al 1997). The use of cannabis is associated with more relapses in schizophrenia with a dose effect relationship; especially heavy use of cannabis was found to be associated with more and earlier relapses (Linszen et al 1994). In addition, cannabis use is associated with low treatment adherence in schizophrenia, leading to more positive symptoms and psychotic episodes (Caspari
et al 1999, Fowler et al 1998, Mueser et al 1990, Regier et al 1990, Soyka et al 1993) and higher rehospitalization rates (Cleghorn et al 1991, Linszen et al 1994, Negrete et al 1986), because cannabis use is associated with medication non compliance (Dixon 1999) and because THC stimulates psychotic symptoms (Caspari et al 1999, Cleghorn et al 1991, Negrete et al 1986). On the other hand, some have shown that cannabis use can alleviate anxiety and negative symptoms in patients with schizophrenia (Dixon et al 1991, Linszen et al 1994). Olanzapine and risperidone may decrease as well as increase craving for and abuse of substances (Hutchison et al 2004, Sayers et al 2005, Smelson et al 2002, 2004). In a 14-week double blind study comparing the efficacy of olanzapine to risperidone in reducing substance craving in individuals with schizophrenia (Akerelle et al 2007), marijuana craving was more likely in the risperidone group than in the olanzapine group. A randomized double blind trial comparing olanzapine and risperidone investigating subjective experience, use of cannabis and craving for cannabis, has not been executed until now. We hypothesize that olanzapine (because olanzapine dissociates faster from the D₂ receptor than risperidone) has a more favorable effect on subjective well-being and therefore on craving for cannabis than risperidone, when tested with doses of antipsychotic medication that lead to comparable dopamine D₂ receptor occupancy (chapter 1.2).

Neuroleptic dysphoria often results in the discontinuation of antipsychotic medication (Garavan et al 1998, Naber et al 2001, van Putten et al 1987). Discontinuation of medication in patients with schizophrenia is also associated with substance abuse (Dixon 1999, Haro et al 2007). The few existing studies that have investigated subjective well-being, substance abuse and treatment continuation until now differ in methodology and are difficult to compare (Lambert et al 2003). Randomized controlled trials comparing olanzapine and risperidone on subjective well-being, craving for cannabis and compliance are lacking. Our hypothesis is that an early dysphoric response to olanzapine or risperidone, and the use of cannabis are important predictors of discontinuation of antipsychotic medication in the first year of treatment (chapter 1.4).

The relationship between improvement of subjective well-being and the enduring symptomatic remission during a five year follow up of first episode schizophrenia is described in chapter 1.5.

Another predictor of poor prognosis in patients with schizophrenia is the co-morbidity of an obsessive-compulsive disorder (OCD) (Berman et al 1998, Fenton et al 1986). OCD is characterized by recurrent, persistent, and intrusive thoughts or images that cause anxiety or distress (obsessions) and/or repetitive behaviors or mental acts aimed at reducing this distress or anxiety (compulsions). The response of OCD patients to selective serotonin re-uptake inhibitors (SSRI’s) has led to the
hypothesis that changes in the central serotonergic systems may be the mechanism by which these compounds exert their effect. Also an increase in dopaminergic system activity in OCD is hypothesized to play a role, since atypical antipsychotics may augment the response to SSRI’s in patients with refractory OCD, and an exacerbation of symptoms occurs after administration of a dopamine agonist. Additionally, several brain regions involved in the pathophysiology of OCD, including the orbitofrontal cortex, striatum, and thalamus, are densely innervated by serotonergic or dopaminergic neurons (van der Wee et al 2004). These brain regions are also thought to be involved in the neurodevelopmental model of schizophrenia. Indeed, there is a relatively high prevalence of obsessive-compulsive symptoms (OCS) in patients with schizophrenia compared to the general population (25-45% vs. 3%) (Berman et al 1995, Fenton et al 1986), and also a relatively high prevalence of OCD: 14% in patients with first episode schizophrenia and 24% in hospitalized patients with chronic schizophrenia (Poyurovsky et al, 1999, 2001, De Haan et al 2002). OCS in patients with schizophrenia can be defined as persistent, repetitive and intrusive and distressful thought (obsessions) not related to the patient’s delusions or repetitive goal-directed rituals (compulsions) clinically distinguishable from schizophrenia mannerisms or posturing (Poyurovsky et al 1999). To distinguish OCS in patients with schizophrenia can approve to be useful if patients with schizophrenia and OCS differ from patients with schizophrenia without OCS in prognosis, treatment response or susceptibility for adverse effects. A major clinical concern is the association of OCS with treatment with type of antipsychotic medication. Previous reports suggest that several atypical antipsychotics may induce or otherwise reduce OCS (Alevizos et al 2002, de Haan et al 1999, 2002, 2004, Eales et al 1994, Jonkers, Mottard et al 1999). The emergence of OCS in patients with schizophrenia receiving atypical antipsychotics has been related to the serotoninergic and dopaminergic interactions of these compounds, particularly the 5-HT2/dopamine antagonistic ratios (Tibbo et al 1999). Previous studies comparing OCS in patients with schizophrenia had methodological limitations. Therefore, we performed a randomized, double blind study comparing the incidence and severity of OCS and OCD of olanzapine and risperidone (chapter 2.1).

Although OCS are increasingly recognized in patients with schizophrenia, little is known about the biological basis to this co-occurrence. The catechol-o-methyl-transferase (COMT) gene is a candidate gene for influencing the expression of the so-called ‘schizo-obsessive diagnostic entity’ (Poyurovsky et al 2005). The COMT gene, involved in the dopamine metabolism in the prefrontal cortex, is located in chromosome 22q11. Patients with micro deletions of this region exhibit a range of psychiatric symptoms, such as psychosis (Murphy et al 1999) and obsessive compulsive disorder (OCD) (Gothelf et al 2004). A common functional polymorphism
in the COMT gene may modify symptom dimensions, especially in disorders where abnormalities in the dopaminergic system are assumed to play a major role (e.g. schizophrenia). The COMT gene contains a functional polymorphism (Val^{158}\text{Met}): the relatively unstable Met/Met variant leads to a 40% decrease in the dopamine degrading enzyme activity in comparison to the Val/Val variant. Although association between the COMT gene and the prevalence of schizophrenia remains controversial (Munafo et al 2005), the functional Val^{158}\text{Met} polymorphism may modulate symptom dimensions within the schizophrenia phenotype (Bilder et al 2004). In this study we investigated the role of COMT as a modifier gene in schizophrenia, i.e. we explored whether there is a relation between the COMT Val^{158}\text{Met} genotype and OCS in a group of patients with recent onset schizophrenia (chapter 2.2).

Finally, co-morbidity involving the metabolic syndrome in schizophrenia has received increasing attention in the recent years. The metabolic syndrome is a combination of medical conditions that increase the risk of developing cardiovascular disease and diabetes (WHO 1999). Symptoms are fasting hyperglycaemia, insulin resistance, high blood pressure, central obesity, decreased HDL cholesterol and elevated triglycerides. Insulin is released postprandial from the beta (\(\beta\)) cells of the pancreas, and it signals insulin-sensitive tissues in the body to absorb glucose to lower blood glucose. Insulin resistance, also known as pre-diabetes, is the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Insulin resistance in fat cells results in elevated hydrolysis of stored triglycerides and therefore in elevated free fatty acids in the blood plasma and insulin resistance in muscle cells reduces glucose uptake and so local storage of glucose (as glycogen). In liver cells the insulin normally gives a signal that glucose production from hepatic glycogen storage should be reduced and thus, insulin resistance in liver cells leads to higher glucose production. High plasma levels of insulin and glucose due to insulin resistance often lead to metabolic syndrome and type 2 diabetes, including its complications.

Recent studies estimate the prevalence of type 2 diabetes mellitus (DM II) among patients with schizophrenia around 10-15\%, which is 2-3 times higher than in the reference population (Holt et al 2005). Moreover, the incidence in patients using antipsychotic medication is estimated between 1.5\% and 4.4\% per year (Citrome et al 2004, Leslie et al 2004). The aetiology of disturbances in glucose metabolism in patients with schizophrenia is uncertain. Influences of factors associated with treatment with antipsychotic medication are important. However, several reports suggest that the vulnerability for disturbances in glucose metabolism may also be associated to the disorder schizophrenia. Recently it was shown that first-episode, drug-naive patients with schizophrenia had higher levels of plasma glucose, insulin, and cortisol than age- and sex- matched controls (Ryan et al 2003). This finding
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could be attributed to differences in body composition between patients with schizophrenia and healthy controls, since a higher waist-to-hip ratio and higher visceral fat content as assessed by computed tomography (CT) scan, were reported in two controlled studies (Ryan et al 2004, Thakore et al 2002). By contrast, in another study, no differences in glucose and insulin concentrations and visceral fat mass were reported in younger drug naive schizophrenic patients compared to healthy controls (Arranz et al 2004, Zhang et al 2004). A recent study using minimal model analysis of an intravenous glucose tolerance test in a rather small number of drug-free patients showed insulin resistance comparable to healthy controls (Cohn et al 2006). These conflicting results may be due to differences in study design or to differences in the definition of insulin sensitivity. The hyperinsulinemic euglycaemic clamp, which is considered as the gold standard to measure insulin resistance (Bergman et al 1979, deFronzo et al 1979), has not been applied yet in drug naive patient with recent onset schizophrenia. The hypothesis of the study described in chapter 3.2 was that drug naive first episode patients have hepatic and peripheral insulin resistance.

Aims of the thesis

- To investigate the effects of olanzapine and risperidone on subjective well-being, craving for and use of cannabis and treatment discontinuation.
- To generate information about the genetic variability associated with obsessive-compulsive symptoms in recent onset schizophrenia, and the effect of atypical antipsychotics on these symptoms.
- To study insulin resistance with the gold standard in neuroleptic naive patients with recent onset schizophrenia.