Chapter 1 Introduction
Mortality and morbidity in patients with severe mental illness

In the last decades all cause mortality of patients with psychotic disorders has increased, while decreasing in the general population. Besides the known higher prevalence of suicide and fatal accidents, patients also have a higher standardized mortality ratio for most natural causes. Correspondingly with the increased mortality, high levels of morbidity have been found in patients with severe mental illness (SMI). The elevated mortality and morbidity can be explained by four main factors. First, the unhealthy lifestyle of patients; many patients smoke, use illicit drugs, have a poor food intake, exercise rarely, and have a sedentary lifestyle. Negative and cognitive symptoms of the psychotic disorder and the prescribing of drugs with sedative effects may contribute to the sedentary lifestyle. Second, the psychotic disorder itself; for example, there is evidence for an elevated prevalence of diabetes mellitus in drug naïve patients with psychotic disorders. Third, patients often do not receive appropriate treatment for their physical diseases. A stigma attached to mental health, perceived barriers to health care services, and a lack of cooperation between health care professionals might explain this reduced utilization of health care services. Fourth, the adverse drug reactions of antipsychotic drugs; the different antipsychotic drugs can to a varying extent cause extrapyramidal symptoms, gastrointestinal complaints, sexual side effects, diabetes, dyslipidemia, and weight gain.

Rational antipsychotic drug treatment

Antipsychotic drugs have been divided based on their different adverse drug reaction profile in first generation (FGA, typical) and second generation (SGA, atypical) antipsychotic drugs. Since 1993 the prescription of antipsychotic drugs and SGAs has increased, while the prescription of FGAs has decreased. Analyzing prescribing patterns of antipsychotic drugs and co-medication in routine practice is important to investigate potentially inappropriate prescribing and risks associated with this practice. Patients receiving FGAs experience more often extrapyramidal symptoms than patients receiving SGAs. SGAs carry an increased risk for developing diabetes, overweight, and dyslipidemia. Clozapine and olanzapine have the highest risk, quetiapine and risperidone a lower risk, and ziprasidone and aripiprazole the lowest risk for these cardiovascular and metabolic adverse drug reactions. Based on the adverse drug profile, a higher adherence has been postulated for
SGAs compared to FGAs.\textsuperscript{14} This is important as adherence rates are particularly low in patients with chronic psychiatric diseases.\textsuperscript{15}

**Metabolic syndrome**

Parallel to the increased market share of SGAs, also the prevalence of obesity, metabolic syndrome and diabetes in patients with psychotic disorders has increased.\textsuperscript{11,16} In an US study antipsychotic drug users had a much higher prevalence of the metabolic syndrome than the general population at the same age.\textsuperscript{17} There are different definitions for the metabolic syndrome (WHO, NCEP/ATP III, ATP IIIa, IDF),\textsuperscript{18-20} but most frequently the definition of the NCEP/ATP III and its variations (IIIa, IDF) have been applied. According to NCEP/ATP III the metabolic syndrome is defined as fulfilling at least three of five dichotomous criteria: hyperglycemia, abdominal obesity, hypertriglyceridemia, hypertension and decreased levels of HDL cholesterol.\textsuperscript{18} The advantage of the concept of the metabolic syndrome is that it is relatively easy to determine in routine practice. Different studies have estimated the prevalence of metabolic syndrome in patients with psychotic disorders.\textsuperscript{17,21-24} Figures ranged between 25\% (Spain)\textsuperscript{21} and 45\% (Canada)\textsuperscript{22}, but so far little work has been done in the Netherlands.

To identify and monitor patients with a cardiovascular and metabolic risk, several countries introduced guidelines for a regular monitoring of the cardiovascular and metabolic risk of patients with psychotic disorders.\textsuperscript{25-27} Based on these guidelines, patients should be screened once a year and more often after antipsychotic drug treatment has been newly started. Long-term follow-up of patients screened on a regular basis will give information on the course of the metabolic syndrome and the specific risk factors associated with the disease. Furthermore the regular monitoring is useful to measure the effect of conducted interventions.

There are three different categories of interventions for patients with an elevated cardiovascular and metabolic risk: lifestyle interventions, cardiovascular/antidiabetic drug treatment, and changes in antipsychotic drugs prescribed. Examples for lifestyle interventions are participating in exercising programs, receiving advice from a dietician, or starting a smoking cessation program. Cardiovascular/antidiabetic drug treatment includes starting anti-diabetic drugs, lipid lowering drugs, or blood pressure lowering drugs. Changes in antipsychotic drug therapy means stopping an antipsychotic drug with a high potential to cause cardiovascular and metabolic side effects (e.g.: clozapine) and starting an
antipsychotic drug with less potential to cause cardiovascular and metabolic side effects (e.g.: aripiprazole). The latter aspect has been studied in randomized controlled clinical trials, but little is known about outcomes in routine practice.

**Other measure to quantify cardiovascular and metabolic risk**

Most studies conducted in patients with psychotic disorders used the metabolic syndrome as a measure for the cardiovascular and metabolic risk. In the general population the metabolic syndrome strongly predicted diabetes, cardiovascular mortality, coronary heart disease mortality and all cause mortality. A much weaker association has been found for coronary heart disease and cardiovascular diseases. There is evidence that cardiovascular and metabolic risk factors cluster together and contribute synergistically to the risk; however it remains unclear if the rather simple definition of the metabolic syndrome describes this correctly. Other measures to quantify risk are cardiovascular risk scores. One of the earliest and best known is the Framingham Risk Score which is based on a long-term epidemiological cohort study in the US. Risk Scores are commonly used as part of cardiovascular risk management guidelines for the general population. Only very recently these scores have been applied to estimate the cardiovascular risk in patients with psychotic disorders.
Scope of the thesis

In the first part of this thesis general aspects related to drug safety in different populations with psychiatric diseases were investigated. Populations were selected based on either the severity of the disease (SMI: severe mental illness) or the situation of living (patients in sheltered housing facilities).

Chapter 2 analyzed pharmacy dispensing data to describe current prescribing patterns in patients with psychiatric diseases living in sheltered housing facilities and raise questions about the rational of prescribing.

Chapter 3 investigated the physical health and adverse drug reactions of patients with severe mental illness. Furthermore we analyzed the health care received by the patients.

Chapter 4 reviewed the published literature on the difference in adherence depending on the type of antipsychotic drug therapy prescribed.

The second part of this thesis focused on the elevated cardiovascular and metabolic risk of patients with psychotic disorders.

Chapter 5 estimated the prevalence of the metabolic syndrome in patients with psychotic disorders in the Netherlands.

Chapter 6 followed the natural course of the metabolic syndrome in patients with psychotic disorders.

Chapter 7 estimated the effects of starting aripiprazole on weight in patients with psychotic disorders.

Chapter 8 analyzed if risk scores can be used to estimate the cardiovascular risk in patients with psychotic disorders.
Chapter 1

References


