Drug safety in patients with psychotic disorders
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Chapter 9 Summary and general discussion
Rational antipsychotic drug treatment and polypharmacy

In the cohorts investigated in this thesis most patients received second generation antipsychotic drugs (SGAs) and only few patients received first generation antipsychotic drugs (FGAs). (Chapter 2, chapter 3, chapter 5, and chapter 6) The SGAs clozapine, olanzapine, and risperidone were the most frequently prescribed antipsychotic drugs. In a cross-sectional study we described the differences between the groups of patients who received different antipsychotic drugs. (Chapter 5) Patients receiving olanzapine were younger and had a shorter duration of disease than patients receiving clozapine. This could explain the lower prevalence of metabolic syndrome in patients receiving olanzapine (olanzapine and clozapine have a similar high risk to cause cardiovascular and metabolic adverse drug reactions). This may indicate that olanzapine was frequently prescribed to younger patients with a low cardiovascular and metabolic risk and patients were switched to another antipsychotic drug once the risk increased. According to guidelines clozapine is prescribed after drug treatment with two other antipsychotic drugs has failed.\textsuperscript{1} It is the most effective antipsychotic drug for treatment resistant schizophrenia\textsuperscript{2} and probably therefore patients were not switched even if their cardiovascular and metabolic risk increased.

A quarter of the patients with psychiatric diseases living in sheltered housing facilities was subject to antipsychotic polypharmacy. (Chapter 2) This was the highest percentage of antipsychotic polypharmacy among the cohorts investigated in this thesis (polypharmacy: 13%-19%). If antipsychotic drugs have a similar adverse drug reaction profile, a combination of antipsychotic drugs increases the risk that drug-drug interactions and adverse drug events occur.\textsuperscript{3} If the adverse drug reaction profiles of the combined drugs are different or if adverse drug reactions are dose dependent and the combination leads to dose reduction, a combination may reduce the risk of adverse drug reactions.\textsuperscript{4} One example is the combination of clozapine and aripiprazole. Clozapine has one of the highest risks for causing weight gain\textsuperscript{5} but, as has been highlighted above, because of the higher efficacy of clozapine psychiatrists might be reluctant to switch patients to another antipsychotic drug. We found that adding aripiprazole to clozapine may lead in some patients to considerable weight loss. Our findings from a non-controlled study were confirmed by a recently conducted randomized controlled trial (RCT).\textsuperscript{6} Patients receiving a combination of aripiprazole and clozapine lost in 16 weeks significantly more weight than patients receiving clozapine and placebo.
Cardiovascular and metabolic risk

The incidence and prevalence of metabolic syndrome

This thesis focused on the cardiovascular and metabolic diseases of patients with psychotic diseases. Around one third (32%, n=138) of the cohort of patients with psychotic diseases fulfilled the criteria for the metabolic syndrome. This prevalence of the metabolic syndrome was considerably higher than in the general population in the Netherlands at a similar age (10%-19%). It was similar to other European populations with psychotic disorders, but lower than in US populations with psychotic disorders. (Chapter 5) We followed part of this population (n=260, 60%) and estimated the prevalence of the metabolic syndrome again after one year. The total prevalence of the metabolic syndrome decreased only slightly in one year follow-up, but major changes occurred on the individual patient level. A substantial number of patients developed (n=21) or reversed (n=30) the metabolic syndrome in one year (incidence 13%, reversal 33%). The variables smoking, a positive family history of cardiovascular or metabolic diseases, and a longer duration of disease were associated with a higher risk of developing the metabolic syndrome, but not with the reversal of the metabolic syndrome.

Consistent with literature, overweight and obesity were the most prevalent cardiovascular and metabolic risk factors: 62% (n=268) of the patients were overweight and 25% (n=109) obese. (Chapter 5) Once patients were overweight they had a much higher risk of developing metabolic syndrome and a much lower chance of reversing it. (Chapter 6) Patients who reversed metabolic syndrome improved on most of the criteria for metabolic syndrome. All other patient groups showed significant deterioration of the lipid and weight criteria in the course of a year. This implies that the majority of the patients worsen gradually, but some of them did not yet reach the cut-off values for the criteria of the metabolic syndrome. A longer follow-up study is necessary in order to analyze and confirm the high incidence and reversal of the metabolic syndrome. Patients who reversed the metabolic syndrome should be followed, in order to investigate if they continue to improve on the variables of the metabolic syndrome or if they develop the metabolic syndrome again.

Interventions to reduce the cardiovascular and metabolic risk

Based on national guidelines, many psychiatric hospitals introduced a regular monitoring of the physical health of patients with psychiatric diseases and/or the users of antipsychotic drugs. The data analyzed in chapter 5, chapter 6, chapter 7, and chapter 8 was collected as
part of such a monitoring scheme, which was part of a disease management program. Regular monitoring is only the first step. Interventions have to be offered to patients for newly identified somatic conditions. Interventions, such as changes in the antipsychotic drugs prescribed, can be conducted directly in the psychiatric hospital. Other interventions such as lifestyle interventions and starting drug treatment for somatic conditions require cooperation with other health care professionals. We investigated the effect of starting aripiprazole treatment on weight. Most patients who continued aripiprazol for 12 months lost weight. Especially female patients benefited from this intervention. But also around one third of the patients discontinued aripiprazole, mainly because their psychiatric symptoms worsened. This indicates that the intervention is only suitable for certain patients. We also investigated if the reversal of the metabolic syndrome within one year was associated with interventions. (Chapter 6) Based on the results of the logistic regression, we could not find such an association. A possible explanation may be the unstructured onset of the interventions between assessments. Furthermore, patients receiving an intervention may have improved, e.g. lost weight, but may not have reached the cut-off level for abdominal obesity as defined by the criteria for the metabolic syndrome. Further research is necessary to investigate which patient characteristics and which other variables are associated with successful interventions in order to know which patients might benefit from a certain intervention.

Quantification of the cardiovascular and metabolic risk

In this thesis different measures for the quantification of the cardiovascular and metabolic risk have been used. The metabolic syndrome has been used to compare our population to other populations (Chapter 5) and to describe its course over one year. (Chapter 6) As discussed above, in our study the dichotomous nature of the criteria of the metabolic syndrome limited its use for the evaluation of interventions. Patients could have improved on a criteria of the metabolic syndrome, but still fulfill the definition of the metabolic syndrome. Furthermore, its association with cardiovascular diseases was rather weak.10 Cardiovascular risk scores have been found to predict cardiovascular risk better than the metabolic syndrome11 and have been recently more frequently applied in patient with psychotic disorders.12-16 When we applied different cardiovascular risk scores in patients with psychotic disorders, the predicted risk varied widely depending on the risk score used. (Chapter 8) This is important as risk prediction might influence the decision to start treatment with cardiovascular medication.17 The variation in risk prediction might be explained by the additional risk factors present in patients with psychotic disorders, such as
antipsychotic drug therapy, and the high cardiovascular risk already present at a young age. (Chapter 8) Therefore, cardiovascular risk scores should not be uncritically applied in patients with psychotic disorders, but further research is necessary. In the short term the distribution and clustering of cardiovascular risk factors in patients with psychotic disorders should be compared to the general population. This might lead to the determination of correction factors for the application of risk scores in patients with psychotic disorders. In the long term a population of patients with psychotic diseases should be followed, in order to describe the course of the disease and identify specific factors which are associated with an increased cardiovascular risk in patients with psychotic disorders.

Health care services for patients with psychiatric diseases
In our study more than one third of patients with SMI had insufficient contact with primary health care professionals. (Chapter 3) This is surprising as physical diseases and symptoms were highly prevalent in this population. Every patient suffered at least from one physical disease or symptom. Our study indicated that there was no regular contact or cooperation between the psychiatric hospital and primary health care services. It was difficult to receive patients’ medical records and medication histories from general practitioners and pharmacies. We received for only 20% of the patients the data requested. Furthermore, we found that pharmacies had often incomplete prescription data. Without complete data on patients’ medication pharmacists are not able to manage drug treatment appropriately. While many patients had regular contact to the psychiatric nurse, this did not result in a referral to another health care professional, e.g. a general practitioner. Druss et al showed that a medical care unit integrated in the psychiatric hospital could improve somatic health of the patients and the quality of care. As already discussed above, interventions to reduce the risk to develop cardiovascular and metabolic diseases require a multidisciplinary approach across the different health care sectors. This should include the pharmacists which have a marginal role in practice so far. Pharmacists should be proactively involved in monitoring the drug treatment of patients with psychiatric diseases. A regular evaluation of patients’ drug therapy and a critical approval of the necessity of each prescribed drug in cooperation with the psychiatric hospital can lead to more rational prescribing for patients with psychotic diseases. General practitioners, pharmacists, psychiatrists and psychiatric nurses should cooperate closely together in order to make somatic treatment easy accessible for patients with psychiatric diseases.
Conclusion

This thesis investigated different aspects of drug safety in the treatment of patients with psychotic disorders. We showed that there is room for improvement in the current prescribing practice for patients with psychiatric diseases. The majority of patients in the cohorts investigated received SGAs. SGAs have been suggested to be related to a better adherence compared to FGAs, but in our systematic literature review, we did not find that adherence differed between patients who received SGAs and those who received FGAs. Adverse drug reactions and somatic diseases were frequent in patients with severe mental illness. We investigated in depth the adverse drug reactions related to an increased cardiovascular and metabolic risk. The prevalence of metabolic syndrome in a cohort of patients with psychotic disorders in the Netherlands was similar to other European countries. Following these patients for one year we found that having the metabolic syndrome is not a static or progressive, but a dynamic condition. Changing antipsychotic drug therapy may lead in some patients to considerable weight loss and can so reduce the cardiovascular and metabolic risk. Finally questions were raised about the uncritical application of cardiovascular risk scores in patients with psychotic disorders.
Summary and general discussion

References


