Summary

Despite the risk of serious adverse effects, antipsychotic drugs are frequently prescribed to elderly patients to relieve psychotic or behavioural symptoms. Antipsychotic induced parkinsonism (AIP), which is characterized by tremor, bradykinesia, rigidity and postural instability during the use of an antipsychotic drug, is an impacting adverse effect affecting about 40% of patients using conventional antipsychotics. Besides that it is well known that elderly people are more prone to develop AIP, there are also notable variations in occurrence of this adverse effect in individual elderly people. Improvement of knowledge about the mechanisms underlying susceptibility for AIP is essential to develop methods to individualize antipsychotic drug therapy that minimizes adverse drug reactions while balancing the need to treat symptoms and maintain well being in the elderly.

The main objective of this thesis was to gain more knowledge about antipsychotic-induced parkinsonism (AIP) in elderly patients. The studies that have been conducted focused on three subjects A) to qualify the available rating scales for drug induced parkinsonism (DIP) and to give a recommendation for use in daily practice, B) to quantify the influence of several potential determinants that may explain variability of AIP, including the role of genetic factors, and C) to investigate consequences of AIP in elderly patients.

Chapter 2 of this thesis describes the assessment of antipsychotic induced parkinsonism. Compared to their widespread use for the assessment of drug induced parkinsonism (DIP), rating scales are seldom sufficiently evaluated for validity and reliability. **Chapter 2.1** provides a systematic review of the available instruments and their clinimetric qualities and feasibility. We identified seventeen different rating scales used for the assessment of DIP. For ten of these we identified validation studies. The most frequently used scale is the Simpson Angus Scale (SAS), followed by the Extrapyramidal Symptom Rating Scale (ESRS) and the Unified Parkinson Disease Rating Scale (UPDRS). None of the indentified scales fulfil all criteria of an appropriate ratings scale for DIP (good conceptual approach, feasible and evidence for validity and reliability). Validation studies for DIP are lacking for the comprehensive UPDRS, which is primarily designed to assess symptoms of Parkinson's disease and not to assess DIP. The SADIMoD has the best evidence for reliability and validity, but it's complexity hampers use in daily practice. The SAS, the St Hans Rating Scale for Extrapyramidal Syndromes (SHRS) and the Drug-Induced Extrapyramidal Symptom Scale (DIEPSS) seem the most valid, reliable and easy to use instruments to evaluate DIP in clinical practice, although it can be questioned whether these rating scales actually measure all aspects of parkinsonism.

Subsequently, we evaluated in **chapter 2.2** the clinimetric properties of the SAS by assessing 15 elderly diagnosed with DIP by three independent investigators. The SAS demonstrated good internal consistency reliability (Cronbach's α coefficients 0.83). We found 87-100% agreement on the individual items with acceptance of one point difference, reflecting good inter-rater reliability. The SAS also demonstrated an acceptable correlation with the SADIMoD (Spearman's rho=0.66; p<0.01). We concluded that the SAS appears to be a valid and by different instructed health care professionals easy to perform research tool to evaluate DIP in daily clinical practice. We decided to use the SAS in our further studies (**chapter 3.1, 3.2 and 4.1**).

Chapter 3 describes factors that possibly influence the variation in occurrence of AIP in elderly patients. Suggested mechanisms underlying increased sensitivity and variation in sensitivity in elderly patients are either higher plasma concentration at a given dose (peripheral pharmacokinetics), an increased brain access and distribution for a given plasma level (central pharmacokinetics), or an increased sensitivity at the receptor level (central pharmacodynamics).

In our very old study population, with mean age of 83 years old we found a prevalence of parkinsonism of 46% during use of haloperidol. In **chapter 3.1** we investigated the association between haloperidol induced parkinsonism (HIP) and dose, plasma concentration and duration of use of haloperidol. Dose of haloperidol was moderate, but significantly associated with haloperidol plasma concentration (weighted r^2=0.32; p<0.001). We found no association between HIP and prescribed dose nor plasma concentration. A not statistically significant trend toward a higher risk with a longer duration of use of haloperidol was observed.

In **chapter 3.2** we investigated whether previous identified genetic polymorphisms at DRD2, ANKK1, DRD3, HTR2A, HTR2C, RGS2, COMT and BDNF genes are associated with AIP in elderly patients. Frequencies of the -759T allele of the HTR2C gene and the 158A allele of the COMT gene were significantly higher in patients without AIP (nominal p=0.03 and p=0.02, respectively). The analysis of the -759 C/T polymorphism was limited to females, since the HTR2C gene is located on the X chromosome and allele frequency calculations of this polymorphism were influenced by gender distribution. Allele carriership in females was associated with a lower risk of AIP (adjusted odds ratio (OR) 0.31; 95% confidence interval (CI) 0.11-0.85). The decrease in risk of AIP in carriers of the COMT 158A allele did not reach statistical significance. Further studies in a larger study population are necessary to investigate whether the 158A allele of the COMT gene has also a protective effect. No significant associations were found between AIP and the remaining selected polymorphisms.

Our study adds to the existing evidence that support is lacking for a major role of the peripheral pharmacokinetic hypothesis in the explanation for the variation in HIP sensitivity in elderly. The results do also not allow a firm conclusion on whether pharmacogenetics is a important factor in the explanation of the increased HIP susceptibility. Further investigation of the central pharmacokinetic hypothesis seems more promising in understanding the increased HIP susceptibility.

Chapter 4 focuses on consequences of AIP in elderly patients.

In **chapter 4.1** we evaluated quality of life in elderly patients with AIP in the same population as in **chapter 3**. Since it is difficult to evaluate the quality of life (QoL) in elderly with poor communication abilities because of psychosis or dementia, we used the QUALIDEM which offers the caregiver the possibility to rate several domains of QoL by observation. We found that the presence of AIP adversely affects the quality of life of elderly patients treated with haloperidol. The presence of AIP resulted in lower scores on QUALIDEM domains assessing positive (mood) and negative (dissatisfaction) affect. Furthermore, on social functioning, measured by observation of social interaction between the patient and other residents, and between patient and caregivers. Lastly, the patients with AIP had less to do, and performed fewer activities without the support of caregivers.

Previous studies suggest that treatment with antipsychotics may increase mortality in elderly. The causes of death appeared to be cardiovascular of infectious (pneumonia). The relation between pneumonia and antipsychotics is not entirely clear. In **chapter 4.2** we investigated the association between antipsychotic drug use and pneumonia in a nested case-control study. We used data from the Dutch PHARMO record linkage system which collates information from community pharmacies and hospital discharge records. After adjusting for confounding current antipsychotic drug use showed an increased risk of pneumonia in elderly people (adjusted OR 1.6; 95% CI 1.3–2.1). This risk is highest in the first week after the initiation. Atypical drugs did not seem to be safer than conventional antipsychotics. The underlying mechanism remains speculative. Impaired oro-pharyngeal bolus transport induced by dryness of the mouth as an anticholinergic effect, excessive sedation as an antihistaminergic effect or extrapyramidal effects on oral pharyngeal musculature causing aspiration are suggested mechanisms. The latter hypothesis seems less plausible as atypical antipsychotics show a stronger association with pneumonia than conventional antipsychotics. This finding implicates a need to monitor elderly patients for swallowing disorders and sedation, particularly at the early phase of treatment with antipsychotics.

Chapter 5 provides a general discussion of the results of the individual studies in this thesis placed in a broader perspective. Three topics are discussed: balancing between limited effectiveness of antipsychotics and serious adverse effects in the elderly; susceptibility for haloperidol induced parkinsonism (HIP) and the gaps in the proposed pathophysiological framework for increased HIP susceptibility; methodological conside-

rations related to research in elderly persons in general and more specifically ralated to pharmacokinetic and pharmacogenetic studies. In addition, implications for clinical practice and research are discussed.

Continued research in elderly people is necesarry to fulfil the expectations of developing effective antipsychotic treatment strategies tailored to the individual older patient.