Antipsychotics are frequently prescribed to older patients for treatment of delirium and behavioural problems in dementia. In the Netherlands there are more than 300,000 antipsychotic users, of which more than 88,000 older than 65 years. However, antipsychotics can have serious adverse effects.

From a pharmacokinetic and pharmacodynamic perspective side effects can be better understood. Most side effects seem to be a group effect and are not limited to a single drug. In chapter 2.1 we investigated a large, not well understood, inter-individual variation in effect and side effects (in particular antipsychotic induced parkinsonism) in older patients. This was studied in haloperidol, the first choice antipsychotic in treatment of delirium. We investigated two possible explanations in pharmacokinetics. First we investigated polymorphisms of the cytochrome P450 CYP2D6, because this contributes to the biotransformation of haloperidol. Second, we investigated variation in transport over the blood-brain barrier (BBB). We included 20 patients >64 years with an elevated risk to develop delirium who were prescribed haloperidol 1mg/day during five days before an elective surgery performed under spinal anaesthesia. Introductory the surgery, cerebrospinal fluid (CSF) (2ml) and a blood sample (2ml) were taken. We found a large inter-individual variation in haloperidol serum concentrations (factor 6). Serum and CSF concentrations of haloperidol averaged 0.52 µg/litre (range 0.17-0.99µg/litre) and 0.04 (range <0.01-0.09µg/litre) respectively (ratio averaged 11.45%). The correlation of CSF and serum concentration was significant (r=0.85, p<0.05). Variation in serum levels haloperidol could not be explained by differences in drug metabolism resulting from polymorphisms of CYPD2D6. Variability in transport over the BBB is not the explanatory factor for inter-individual variation in response. An alternative explanation is the number of remaining dopamine-2 receptors in the brain.

In chapter 2.2 we investigated whether factors of thrombogenesis are activated in older, non-psychotic hospitalised patients treated with haloperidol.
We wanted to reveal the underlying mechanism of the increase in (cerebro) vascular events in older antipsychotic users. With a subset of patients included in a randomised, stratified, double-blind, placebo-controlled trial “Haloperidol prophylaxis in older emergency department patients” HARPOON study we studied this research question. This subset of patients consisted of all the patients that were included in the Jeroen Bosch Hospital between June 2014 and March 2015. Patients >70 years with an increased risk of developing delirium, according to the “VMS criteria”, were randomised to haloperidol 1mg twice a day or placebo. Before the start of haloperidol and at day 6, after 10 gifts of haloperidol, blood was collected. In the Jeroen Bosch Hospital we analysed 16 patients that received haloperidol in comparison to 18 patients that received placebo. There were no significant changes in levels of markers of thrombogenesis fibrinogen and D-dimer, p-selectin as marker of platelet activation, and von Willebrand factor and osteoprotegerin as markers of endothelial activation between the haloperidol and the placebo group. We did find a significant difference in both groups over time, between day 1 and day 6, in which haloperidol is not the direct cause of changes in trombogenic factors. Fibrinogen increased significant during the hospital stay and P-selectin decreased significant in both groups over time. Possibly there are indirect factors that are related to the disease or hospital admission that could be the explanation. Thus the underlying cause of the increase in cerebrovascular events seen in haloperidol users remains to be established.

In chapter 3 we investigated different side effects in frail older patients in clinical practice. Falls in the elderly are common and often serious. The general message that psychotropic drugs increase falls is already well accepted. However, the contribution of specific psychotropic drugs to fall frequency in elderly has not been quantified precisely until now. We describe this in chapter 3.1. Between 1st January 2011 and 1st April 2012 416 patients visited the day clinic of the department of geriatric medicine of the University Medical Centre Utrecht. Psychotropic medication use was present in one third (34%) of the patients. Patients who used psychotropic medications had a significant lower gait speed on the 4 meter walk test (0.8 versus 0.9m/second, p-value 0.041) and lower isometric grip strength (29.3 versus 37.9kg, p-value 0.001) compared to non users. Frequent falling, at least more than two time in the past year, was after correction for confounders a risk factor in antipsychotic users (OR 3.62, 95% CI 1.27-10.33). Hypnotic and anxiolytic medication use was significantly associated with frequent falls (OR 1.81; 95% CI 1.05-3.11) as well as short-acting
benzodiazepines or Z-drugs use (OR 1.94, 95% CI 1.10-3.42) and antidepressant use (OR 2.35, 95% CI 1.33-4.16). The use of different groups of psychotropic medication was strongly associated with falls. This relation should be explicitly recognised by doctors prescribing for older people, and by older people themselves. If possible such medication should be avoided for elderly patients especially with other risk factors for falling.

Over the last decade new side effects in antipsychotic medication are still found. In previous studies it is suggested that treatment with antipsychotics increases the risk of mortality in older patients. Although the cause of this increased mortality is not completely understood, antipsychotic drug use is associated with an increased risk of cardiovascular events, such as stroke, thrombo-embolic events, and cardiac arrhythmia, and infections, such as pneumonia. In chapter 3.2 we investigated the association between urinary tract infections (UTIs) and antipsychotic drug use in older women. In a cohort study between 1998 and 2008 we looked at recurrent prescriptions of nitrofurantoin, as representation for uncomplicated UTI in women >65 years. Person time for current use of antipsychotic was compared to past use of an antipsychotic. For this study we used data from the PHARMO Database Network. The PHARMO database network includes the pharmacy dispensing records of community dwelling residents in the Netherlands. In total 18,541 women were followed from their first prescription of an antipsychotic till the end of their registration in the database or the end of the study period. Current use of antipsychotics was associated with a 33% increased risk of UTIs compared with past use (adjusted for age and history of urinary tract infections HR 1.33, 95% CI 1.27-1.39). The risk of getting a UTI was higher in the first week after start of the antipsychotic medication (adjusted HR 3.03, 95% CI 2.63-3.50). Conventional antipsychotics showed a slightly higher point estimator (HR 1.36, 95% CI 1.30-1.43) than atypical antipsychotics (HR 1.22, 95% CI 1.13-1.30). As we did not have access to clinical data, the presence of a urinary tract infection was based on the prescription of nitrofurantoin, which could have led to misclassification. In general, Dutch physicians are reluctant to prescribe antimicrobial drugs because of the risk of resistance, and treat only those patients with a proven or very high suspicion of infection. Complicated UTIs are treated with antibiotics that reach urine and tissue, such as fluoroquinolones, and so we cannot generalize our findings to complicated urinary tract infections. The association between uncomplicated UTIs and antipsychotic use is probably an underestimation, because antibiotics other than nitrofurantoin are also prescribed for uncomplicated urinary tract infections. If these findings were also generalisable to men and to complicated
urinary tract infections we studied this research question in chapter 3.3. For this study we used the Clinical Practice Research Datalink (CPRD). This is an anonymised database containing approximately 12 million complete electronic medical records from over 600 participation general practices across the United Kingdom. Primary care diagnoses, prescriptions, laboratory test results, referrals and patient demographics are recorded in the CPRD using a hierarchical clinical coding system (Read codes). In this cohort study we also looked at recurrent urinary tract infections in older antipsychotic users. During the study period, 191,827 patients (63.7% women, mean age 77 years) with a first prescription of an oral antipsychotic drug were identified. Current use of antipsychotics was associated with an increased risk of UTI compared with past use (adjusted HR 1.31, 95% CI 1.28-1.34). The strongest effect was found within the first 14 days after the start of the antipsychotic (adjusted HR 1.83, 95% CI 1.73-1.95) and for patients with more than one antipsychotic drug concomitantly (adjusted HR 1.64, 95% CI 1.45-1.87). The risk was slightly higher for conventional antipsychotics (adjusted HR 1.37, 95% CI 1.33-1.41) compared to atypical antipsychotics (adjusted HR 1.24, 95% CI 1.21-1.28). Stratification by sex showed that risk estimates were slightly higher in men than in women.

The mechanism how antipsychotics cause urinary tract infections is unknown. D2-receptor antagonists have been suggested to influence the capacity and residual volume of the bladder. Anticholinergic side effects of antipsychotic medication are another cause of urine retention. The retention of urine, which can lead to bacterial growth, possibly underlies the increase in uncomplicated UTI. Doctors should be alert to the occurrence of UTIs in both men and women after the start of an antipsychotic drug, especially in the first two weeks.

In chapter 4 we focus on the recognition and measurement of side effects in antipsychotics. As described before in this thesis, unfortunately, many patients experience side effects during treatment, which may result in an impaired quality of life and early treatment discontinuation. Adverse drug reactions are frequently missed, either because clinicians do not always ask about them or do not recognize complaints as possible side effects. There can be some discrepancies between the distress associated with certain side-effects by prescribers and consumers of antipsychotic drugs and the fact that patients are unlikely to attribute symptoms as side effects of antipsychotic medication. In this chapter we give an overview of all available scales to measure side effects in antipsychotics. Psychometric characteristics are described in terms of reliability and validity. Reliability is the extend in which results are influenced by accidental conditions. Validity is the extend that the test measures what it should
measure and what you really want to know. Some scales are used frequently, but psychometric characteristics are not always well described. Other scales are reliable and valid, but are almost never used in clinical practice. In total, we found 52 different scales that measure side effects of antipsychotics. To measure multi-domain side effects the Udvalg for Kliniske Undersøgelser Side Effects Rating Scale for Clinicians (UKU-SERS-Clin) was used the most. The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) had the best psychometric characteristics (Cronbach’s $\alpha$ 0.81 and test-retest reliability 0.89). The Glasgow Antipsychotic Side effect Scale (GASS) is the fastest and takes 5 minutes to complete. The scales differ in number of items that are scored, the time to complete the scale and if the scale is filled out by the patient self or by the clinician. The Simpson Angus Scale (SAS), followed by the Abnormal Involuntary Movements Scale (AIMS) and the Barnes Akathisie Rating Scale (BARS) were used the most to assess extrapyramidal side effects, however the Maryland Psychiatric Research Center scale (MPRC scale) had the best characteristics (Cronbach’s $\alpha$ 0.80, test-retest reliability 0.92 and inter-rater reliability 0.81-0.90). The Arizona Sexual Experience Scale (ASEX) was used the most to measure sexual dysfunction, but the Antipsychotics and Sexual functioning Questionnaire (ASFQ) and the Nagoya Sexual Functioning Questionnaire had the best characteristics. It should be noted that potentially life threatening side effects such as neuroleptic malignant syndrome, significant QTc prolongation are also very important, although they fail to be captured with the existing rating scales. The prescribing physician should consider basing the selection of antipsychotics in light of the differences in side effects profiles, rather than those in antipsychotic efficacy. The prescribing physician should monitor adverse drug reactions and can use one of the scales above.

Finally chapter 5 describes a general discussion where the individual studies of this thesis are placed in a broader perspective.